# 13. INTEGRATIVE SYNTHESIS OF KEY POINTS: PM EXPOSURE, DOSIMETRY, AND HEALTH RISKS

## 13.1 INTRODUCTION

This chapter integrates key information on exposure-dose-response risk assessment components drawn from the preceding detailed chapters, in order to provide a coherent framework for assessment of human health risks posed by ambient particulate matter (PM) in the United States. More specifically, this chapter first provides background information on key features of atmospheric particles, highlighting important distinctions between fine and coarse mode particles with regard to their size, chemical composition, sources, atmospheric behavior, and potential human exposure relationships—distinctions which collectively suggest that fine and coarse mode particles should be treated as two distinct subclasses of air pollutants. Information on recent trends in U.S. concentrations of different ambient PM size/composition fractions and ranges of variability seen in U.S. regions and urban air sheds is also summarized to place the ensuing health effects discussions in perspective.

The chapter next summarizes key points regarding respiratory tract dosimetry, followed by discussion of the extensive PM epidemiologic database that has evolved during the past several decades. The latter includes recent studies providing evidence that serious health effects (mortality, exacerbation of chronic disease, increased hospital admissions, etc.) are associated with exposures to ambient levels of PM found in contemporary U.S. urban air sheds even at concentrations below current U.S. PM standards. Evaluations of other possible explanations for the reported PM epidemiology results (e.g., effects of weather, other co-pollutants, choice of models, etc.) are also discussed, ultimately leading to the conclusion that the reported associations of PM exposure and effects are valid. Evidence is then reviewed that (a) clearly substantiates associations of such serious health effects with U.S. ambient $PM_{10}$ levels and (b) less extensively points toward fine particles (as indexed by various indicators) as likely being important contributors to the observed human health effects. The overall coherence of the epidemiologic data base is also discussed, suggesting a likely causal role of ambient PM in contributing to the reported effects.

The nature of the observed effects and hypothesized potential mechanisms of action underlying such effects are then discussed in subsequent sections. The discussion of potential mechanisms of injury examines ways in which PM could induce health effects. The current limited availability of much experimental evidence necessary to evaluate or directly substantiate the viability of the hypothesized mechanisms is noted. Limited information concerning possible contributions of particular classes of specific ambient PM constituents is also summarized.

The chapter also provides information on the identification of population groups at special risk for ambient PM effects, factors placing them at increased risk, and other key components that need to be considered in generating risk estimates for the possible occurrence of PM-related health events in the United States. An examination of risk factors includes those affecting exposure risk and mechanistic determinants of dose, as well as individual factors affecting susceptibility related to age or disease.

One of the present problems of “integrating” PM health effects research results is the current disparity between evidence from epidemiologic studies and from experimental human exposure and laboratory animal studies. On the one hand, epidemiologists have examined relationships between regionally and temporally variable mixtures of ambient air particles and broad classes of health effects (e.g., mortality, hospital admissions, respiratory illness, etc.), whose target population largely includes the elderly and individuals with cardiopulmonary disease. Extremely high exposure levels associated with historic air pollution "disasters" indicate that severe illness and death are clearly linked with high levels of air pollution, including PM. Also, children have been studied for respiratory symptomatology and mechanical pulmonary function changes in relation to ambient PM concentrations. On the other hand, experimental human studies have focused mainly on reversible physiologic and biochemical effects in young healthy people that result from controlled exposures to laboratory-generated acidic aerosols, sulfates or nitrates. Laboratory animal studies cover a broader range of specific health endpoints than the human studies, but again typically evaluate individual particle species that comprise the ambient mixture called particulate matter and their effects on healthy animals. Much more experimental research data are needed on effects of ambient (or quasi-ambient) PM on diseased humans or animal models of disease.

## 13.2 AIRBORNE PARTICLES: DISTINCTIONS BETWEEN FINE AND COARSE PARTICLES AS SEPARATE POLLUTANT SUBCLASSES

As discussed in detail in Chapter 3 of this document, airborne PM is not a single pollutant but many classes of pollutants, each class consisting of several to many individual chemical species. One classification is based on the natural division of the atmospheric aerosol into fine-mode and coarse-mode particles. Fine-mode particles, in general, are smaller than coarse-mode particles, but they also differ in many other aspects such as formation mechanisms, chemical composition, sources, physical behavior, human exposure relationships, and control approaches required for risk reduction. Such differences alone are sufficient to justify consideration of fine-mode and coarse-mode particles as separate pollutants, regardless of the extent or lack of evidence regarding differences in composition, respiratory tract dosimetry, or associated health effects in laboratory animals or humans. Table 13-1 compares several key points that differentiate fine-mode and coarse-mode particles. Various physical and chemical differences between fine-mode particles and coarse-mode particles, their sources, factors affecting human exposure, and their respiratory tract deposition are also concisely summarized below as a prelude to more in-depth discussion of key health effects associated with ambient PM exposures and other information useful in assessing PM-related public health risks in the United States.

### 13.2.1 Size Distinctions

Three approaches are used to classify particles by size: (1) modes, based on formation mechanisms and the modal structure observed in the atmosphere; (2) size cut point, based on the 50% cut point of the specific sampling device; and (3) dosimetry, based on the ability of particles to enter certain regions of the respiratory tract. The modal structure is shown in Figure 13-1. In the ambient atmosphere the fine particle mode is composed of the nuclei mode and the accumulation mode. The nuclei mode is clearly observable only near sources of condensible gases. Particles in the nuclei mode rapidly grow into the accumulation mode but the accumulation mode does not grow further into the coarse particle mode. The lognormal distribution (in units of particle diameter) is frequently used to approximate the distribution of particle number, surface area, volume, or mass. The accumulation mode may contain varying amounts of ultrafine particles ($\leq 0.1$ $\mu$m) aggregated from the nuclei mode.

**TABLE 13-1. COMPARISON OF AMBIENT FINE AND COARSE MODE PARTICLES**

| | Fine | Coarse |
|---|---|---|
| Formed from: | Gases | Large solids/droplets |
| Formed by: | Chemical reaction<br>Nucleation<br>Condensation<br>Coagulation<br>Evaporation of fog and cloud droplets in which gases have dissolved and reacted | Mechanical disruption (crushing, grinding, abrasion of surfaces, etc.)<br>Evaporation of sprays<br>Suspension of dusts |
| Composed of: | Sulfate, $SO_4^=$<br>Nitrate, $NO_3^-$<br>Ammonium, $NH_4^+$<br>Hydrogen ion, $H^+$<br>Elemental carbon,<br>Organic compounds (e.g., PAHs, PNAs)<br>Metals, (e.g., Pb, Cd, V, Ni, Cu, Zn, Mn, Fe)<br>Particle-bound water | Resuspended dusts (Soil dust, street dust)<br>Coal and oil fly ash<br>Oxides of crustal elements, (Si, Al, Ti, Fe) $CaCO_3$, NaCl, sea salt<br>Pollen, mold, fungal spores<br>Plant/animal fragments<br>Tire wear debris |
| Solubility: | Largely soluble, hygroscopic and deliquescent | Largely insoluble and non-hygroscopic |
| Sources: | Combustion of coal, oil, gasoline, diesel, wood<br>Atmospheric transformation products of $NO_x$, $SO_2$, and organic compounds including biogenic organic species, e.g., terpenes<br>High temperature processes, smelters, steel mills, etc. | Resuspension of industrial dust and soil tracked onto roads and streets<br>Suspension from disturbed soil, e.g., farming, mining, unpaved roads<br>Biological sources<br>Construction and demolition, coal and oil combustion, ocean spray |
| Atmospheric half-life: | Days to weeks | Minutes to hours |
| Travel distance: | 100s to 1000s of km | <1 to 10s of km |

Source: Adapted from Wilson and Suh (1996).

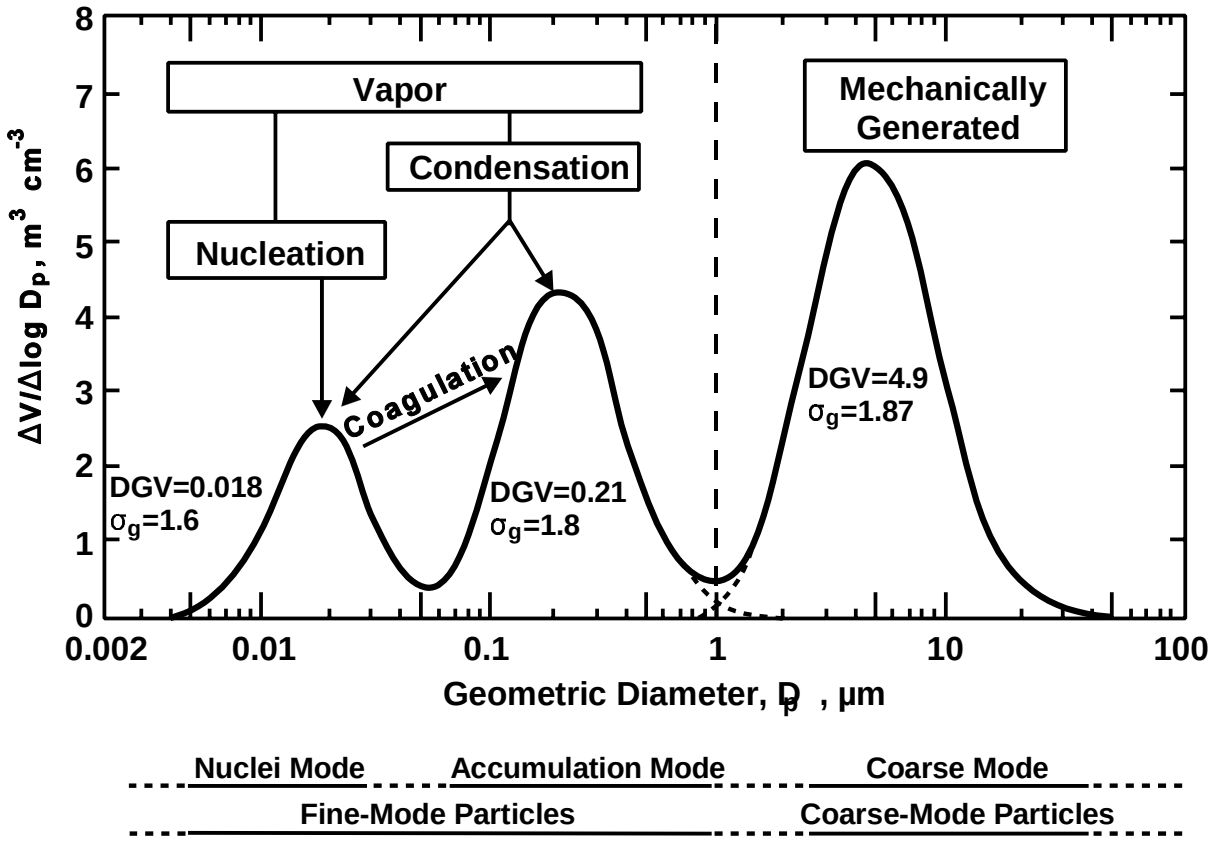


**Figure 13-1. Measured volume size distribution showing fine-mode and coarse-mode particles and the nuclei and accumulation modes within the fine-particle mode. DGV (geometric mean diameter by volume, equivalent to volume median diameter) and $\sigma_g$ (geometric standard deviation) are shown for each mode. Also shown are transformation and growth mechanisms (e.g., nucleation, condensation, and coagulation).**

Source: Wilson et al. (1977).

Particle diameters are usually given as aerodynamic equivalent diameter, $d_{ae}$, defined as the diameter of a particle with equal settling velocity to that of a sphere with unit density (1 g/cm$^3$). This is the most appropriate diameter for discussion of lung deposition and particle collection. The accumulation mode typically has a mass median aerodynamic diameter (MMAD) of 0.3 to 0.7$\mu$m and a geometric standard deviation, $\sigma_g$ (a measure of the size dispersion), of 1.5 to 1.8. The coarse particle mode may also contain multiple modes but they are not readily distinguished. Therefore, the coarse particle mode tends to have a broader size distribution, with a $\sigma_g$ = 2.2 to 2.4. Measured MMADs typically range from 6 to 20 $\mu$m diameter in the ambient

atmosphere, but these values may be low because of the difficulty of collecting particles in the upper tail of the coarse-mode distribution.

The indicator for the current PM standard is $PM_{10}$. Since neither the respiratory tract nor particle samplers can separate particles with a sharp cut, $PM_{10}$ is defined as having a 50% cutpoint at 10 $\mu$m $d_{ae}$. $PM_{10}$ samplers collect all fine-mode particles. They collect a decreasing fraction of particles as the diameter increases above 10 $\mu$m $d_{ae}$ and an increasing fraction of particles as the diameter decreases below 10 $\mu$m $d_{ae}$. The mass of the coarse fraction ranges from 20% of $PM_{10}$ in some eastern urban areas to 80% of $PM_{10}$ in dry western areas.

Agreement has been reached between the International Standards Organization (ISO) and American Council of Government Industrial Hygienists (ACGIH) who have also promulgated definitions of particle size fractions that are based on the ability of particles to penetrate to various depths within the respiratory tract (Vincent, 1995). Inhalable refers to particles which can enter beyond the external airway openings and, as discussed in Chapter 10, has a practical upper limit of 40 to 60 $\mu$m. Thoracic particles refer to those particles which can penetrate beyond the larynx; 50% of particles of 10 $\mu$m aerodynamic diameter will penetrate beyond the larynx.

The appropriate division between the fine and coarse fractions is not sharply defined, but falls in the range between 1.0 and 3.0 $\mu$m $d_{ae}$, where fine-mode and coarse-mode particles overlap but where particle mass is at a minimum. Thus, in general, particles less than 1.0 $\mu$m $d_{ae}$ are fine-mode particles and particles greater than 2.5$\mu$m $d_{ae}$ are coarse-mode particles. However, as the relative humidity approaches 100%, fine particles may grow beyond 1.0 $\mu$m and even beyond 2.5 $\mu$m $d_{ae}$; and, in very dry environments, it may also be possible to find particles less than 1.0 $\mu$m $d_{ae}$ in the small size tail of the coarse particle mode. It is important to note that $PM_{2.5}$ may sometimes contain an appreciable quantity of coarse-mode particles in the 1 to 2.5 $\mu$m $d_{ae}$ size range.

$PM_{2.5}$ particles are frequently referred to as fine, while the difference between $PM_{2.5}$ and $PM_{10}$ ($PM_{10-2.5}$), is sometimes referred to as coarse or as the coarse fraction of $PM_{10}$. In the present discussion, fine-mode particles and coarse-mode particles are used to emphasize that important distinctions include not just size but also other additional fundamental differences in sources, formation mechanisms, and chemical composition.

### 13.2.2 Formation Mechanisms

Fine particles are formed from gases by nucleation (gas molecules coming together to form a new particle), by condensation (gas molecules condensing onto a pre-existing particle), or by liquid phase reactions. Gases may dissolve in a liquid droplet (either a solution particle or a cloud or fog droplet), react with another dissolved gas, and form a low vapor pressure product. When fog and cloud droplets evaporate, particulate matter remains, usually in the fine particle mode.

Coarse particles are formed by mechanical processes which produce small particles from large ones. Energy considerations normally limit coarse mode particle sizes to greater than about 1.0 $\mu$m $d_{ae}$.

Particles are designated as primary if they are emitted directly into the air as particles or as vapors which condense to form particles without chemical reaction. Examples of primary particles are (a) elemental carbon chain agglomerates formed during combustion and (b) chemical species such as lead, cadmium, selenium, or sulfuric acid which are volatile at combustion temperature but form PM rapidly as the combustion gases cool.

Particles are designated as secondary if they form following a chemical reaction in the atmosphere which converts a gaseous precursor to a product which either has a low enough saturation vapor pressure to form a particle or reacts further to form a low saturation vapor pressure product. Examples are the conversion of sulfur dioxide ($SO_2$) to sulfuric acid ($H_2SO_4$) which nucleates or condenses on existing particles, or the conversion of nitrogen dioxide ($NO_2$) to nitric acid ($HNO_3$) which may react further with ammonia ($NH_3$) to form particulate ammonium nitrate ($NH_4NO_3$).

Coarse particles are normally primary since they are formed by mechanical rather than by chemical processes. An exception is the reaction of acid gases with carbonate ($CO_3^=$) containing particles in which the $CO_3^=$ may be replaced by sulfate ($SO_4^=$), nitrate ($NO_3^-$), or chloride ($Cl^-$). Other exceptions are the reaction of $HNO_3$ with NaCl to form $NaNO_3$ and HCl gas and the reaction of $SO_2$ with wet NaCl to form $Na_2SO_4$ and HCl gas.

## 13.2.3 Chemical Composition

### 13.2.3.1 Fine-Mode Particulate Matter

In the ambient atmosphere, fine-mode particulate matter is mainly composed of varying proportions of six major components (sulfates, acids, nitrates, elemental carbon, organic carbon, and trace elements such as metals) and varying amounts of water.

***Sulfates/Acid.*** Sulfur dioxide ($SO_2$), mainly from combustion of fossil fuel, is oxidized in the atmosphere to form sulfuric acid ($H_2SO_4$) particles. The $H_2SO_4$ may be partially or completely neutralized by reaction with ammonia ($NH_3$). Since the particles usually contain water, the actual species present are $H^+$, $HSO_4^-$, $SO_4^=$, and $NH_4^+$, in varying proportions depending on the amount of $NH_3$ available to neutralize the $H_2SO_4$. Particle strong acidity is due to free $H^+$ or $H^+$ available from $HSO_4^-$ or $H_2SO_4$.

***Nitrates.*** Nitrogen oxides ($NO_x$= NO + $NO_2$) are formed during combustion or any high temperature process involving air. The NO is converted to $NO_2$ by ozone ($O_3$) or other atmospheric oxidants. During the daytime, $NO_2$ reacts with the hydroxyl radical (OH) to form nitric acid ($HNO_3$). During nighttime, it forms nitric acid through a sequence of reactions involving ozone and the nitrate radical ($NO_3$). Ammonia reacts preferentially with sulfuric acid, but, if sufficient $NH_3$ is available, particulate ammonium nitrate ($NH_4NO_3$) will form.

***Elemental Carbon.*** Chain agglomerates of very small elemental carbon (EC) particles are formed during combustion, such as in open hearth fireplaces, wood stoves and diesel engines.

***Organic Carbon.*** Several heterogenous categories of organic carbon (OC) compounds are also often found in ambient air, as follows:

- **Primary-anthropogenic.** Incomplete combustion also leads to hundreds of organic compounds with low enough vapor pressure to be present in the atmosphere as particles, including mutagenic species such as polyaromatic hydrocarbons (PAHs).
- **Secondary-anthropogenic.** Some organic compounds, including aromatics (larger than benzene), cyclic olefins and diolefins, and other $C_7$ or higher hydrocarbons, react with $O_3$ or OH to form polar, oxygenated compounds with vapor pressures low enough to form particles.

- **Primary biogenic.** Viruses, some bacteria, and plant and/or animal cell fragments may be found in the fine mode.
    - **Secondary biogenic.** Terpenes, $C_{10}$ cyclic olefins released by plants, also react in the atmosphere to yield organic particulate matter.

***Trace Elements.*** A variety of transition metals and non-metals are volatilized during the combustion of fossil fuels, smelting of ores, and incineration of wastes and are emitted as fine particles (or vapors which rapidly form fine particles).

***Water.*** Sulfates, nitrates, and some organic compounds are hygroscopic, i.e., they absorb water and form solution droplets. A variety of atmospheric pollutant gases can dissolve in the water component of the particle. This provides a mechanism for carrying into the lung species such as $SO_2$, $H_2O_2$, HCHO, etc., which, when in the gas phase, would normally be removed in the nose, throat, or upper airways.

### 13.2.3.2 Coarse-Mode Particulate Matter

Coarse-mode PM sources are primarily crustal, biological, or industrial in nature.

***Crustal.*** Crustal material, from soil or rock, primarily consists of compounds that contain Si, Al, Fe, Mg, and K (small amounts of Fe and K are also found among fine-mode particles but come from different sources). In urban areas, much crustal material arises from soil which is tracked onto roads during wet periods and is suspended in the air by vehicular traffic. In rural areas, tilling, wind blowing over disturbed soil, or vehicles traveling on unpaved roads can generate coarse particles. Where farms have been treated with persistent pesticides or herbicides, these materials may also be present in suspended soil particles.

***Biological.*** Biological materials such as bacteria, pollen, spores, and other plant and animal fragments are mostly found in the coarse size range (i.e., 2.0 to 10 $\mu$m $d_{ae}$ for most, >20 $\mu$m $d_{ae}$ for some).

***Industrial.*** A variety of industrial operations generate coarse particles. Examples are construction and demolition, open pit mining, grain handling, coal handling, etc. Also, coal and oil combustion generate fly ash which is similar in chemical composition to soil and crustal material but can be differentiated by microscopic examination.

### 13.2.4 Atmospheric Behavior

Coarse-mode particles are large enough so that the force of gravity exceeds the buoyancy forces of the air. Therefore, large particles tend to rapidly fall out of the air. Coarse-mode particles are also too large to follow air streams, so they tend to be easily removed by impaction on surfaces. The atmospheric half-life of coarse particles depends on their size, but is usually only minutes to hours. However, vigorous mixing and convection, such as occurs during dust storms, can lead to longer lifetimes for the smaller size range of coarse-mode particles.

In contrast, fine-mode particles are small enough that gravitational forces are largely overcome by the random forces from collisions with gas molecules. Thus fine particles tend to follow air streams and are typically not removed by impaction. Accumulation-mode particles are sufficiently larger than gas molecules that their diffusion velocity is low. Removal by dry deposition is inefficient since they do not readily diffuse through the boundary layer of still air next to surfaces. Therefore, accumulation-mode particles have very long half-lives in the atmosphere, travel long distances, and tend to be more uniformly distributed over large geographic areas than coarse-mode particles. The atmospheric half-life of accumulation-mode particles with respect to dry deposition is on the order of weeks. Removal of accumulation-mode particles occurs when the particles absorb water, grow into cloud droplets, grow further to rain drops, and fall out as rain. This process reduces the atmospheric half-life of accumulation-mode particles to a few days.

Ultrafine or nuclei-mode particles, formed by nucleation of low saturation-vapor-pressure substances, tend to exist as disaggregated individual particles for very short periods of time (<minutes) in the ambient atmosphere due to rapid aggregation into accumulation- mode particles. Thus, ultrafine or nuclei-mode particles, possibly present in continuously supplied high concentrations near high temperature sources, tend to age rapidly into larger accumulation-mode particles that may be dispersed more widely over long distances.

### 13.2.5 Sources

The nature of fine and coarse PM sources are very different. Fine particulate matter is produced mainly by the condensation of gases in the high temperature environment of combustion chambers; the condensation of atmospheric precursor gases, some of which may undergo further reactions in particles; and the condensation of low vapor pressure photochemical

reaction products. Coarse particles, on the other hand, are produced mainly by the abrasion of surfaces (e.g., wind erosion, tire friction).

For a variety of reasons, concentrations of aerosol constituents measured at specific monitoring sites do not reflect the composition that would be obtained from a straightforward comparison of the source strengths shown in Chapter 5. Although windblown dust, from whatever source, represents the largest single category of $PM_{10}$ emissions by mass (accounting for roughly 88% of the total), it does not often account for more than half of the mass of ambient samples. This discrepancy reflects in part the shorter residence time of dust in the atmosphere. Dust is found mainly in the coarse fraction, while secondary constituents are mainly found in the fine fraction. Monitoring sites are frequently located near specific sources such as roadways and less frequently away from areas where there is a perceived need for monitoring.

In general, emissions of primary $PM_{10}$ components and gaseous precursors to $PM_{10}$ are estimated to have decreased from 1984 to 1993. Ambient $PM_{10}$ levels have also decreased in major urban areas during the same time period. However, a number of factors preclude a detailed comparison between trends in $PM_{10}$ emissions and trends in ambient $PM_{10}$ levels. These factors include long term variations in transformation rates of precursor gases to secondary particulate matter, wet and dry deposition rates, and effects of meteorological variability on dust emissions. As an example, nationwide emissions of dust by wind erosion decreased by almost a factor of eight between 1992 and 1993, because of the severe wet weather in the central United States. The large effect of meteorological variability on the magnitude of fugitive dust places severe constraints on the magnitude of trends in ambient dust concentrations that can be discerned. Because of the large secondary component of $PM_{10}$ in the eastern United States, the concentration of $PM_{10}$ reflects the emission of gaseous precursors by widely dispersed sources, followed by their conversion to particulate matter. The conversion of gases to secondary particulate matter occurs over distances of up to a few thousand kilometers, thereby uncoupling variability in the emissions of local sources from that of ambient concentrations.

## 13.2.6 Patterns and Trends in United States Particulate Matter Concentrations

### *$PM_{10}$ Trends and Concentrations*

Annual average $PM_{10}$ mass concentrations throughout the United States, for different regions within the United States, and for most subregions or cities have generally decreased from 1988 to 1994. For the contiguous United States, the $PM_{10}$ decrease has been greater in the western United States (approximately 30%) than in the eastern United States (about 15 to 20%). With few exceptions, the same range of percentage decreases have occurred for most subregions within the eastern and western United States. Smaller decreases in $PM_{10}$ concentrations occurred for a few eastern subregions or cities and larger decreases in $PM_{10}$ occurred for a few cities in the west. These decreases in annual average $PM_{10}$ levels ranged from 25 to 35 $\mu g/m^3$ for all U.S. regions and most U.S. cities by 1994.

In general, annual mean $PM_{10}$ concentrations in urban areas, found in EPA's Air Information Retrieval System (AIRS, 1995) database, are greater than about 20 $\mu g/m^3$. The highest annual mean concentrations in the eastern United States were found in Atlanta, GA; Paterson, NJ; Roanoke, VA; Philadelphia, PA; and Atlantic City, NJ. The overall annual mean concentration from these urban areas was about 34 $\mu g/m^3$. The five urban areas in the central United States with the highest annual mean concentrations were St. Joseph, MO; Steubenville, OH; Cleveland, OH; Omaha, NE; and Chattanooga, TN. The overall annual mean $PM_{10}$ concentration for these five cities was 36 $\mu g/m^3$. The five areas with the highest annual mean $PM_{10}$ concentrations in the western United States were Bakersfield, CA; Visalia, CA; Fresno, CA; Riverside, CA; and Stockton, CA. The average concentration in these five areas was about 50 $\mu g/m^3$. This value is significantly higher than corresponding values in the eastern and central United States. All averages given above were taken over the five year period from 1990 to 1994. At least one monitoring site was located in each area listed above, most areas had data from several sites. The sites themselves are located in areas representing a variety of different activities (e.g., industrial, commercial, agricultural and residential). The lowest annual mean $PM_{10}$ concentrations found at sites in populated areas in the United States (Penobscot Co., ME; Marquette, MI; and Lakeport, CA) averaged about 12 $\mu g/m^3$ during the period from 1990 to 1994. Concentrations in all other areas in the United States fell within the limits given above.

All of the annual means stated above were calculated on the basis of sampling schedules that varied from every day to every sixth day, depending on the likelihood of exceedances of the $PM_{10}$ NAAQS. The range of annual mean values shown above is consistent with the range found at the central sites used in the Harvard Six-City Study, where measurements were made every other day. The six cities along with their annual means are: Steubenville, OH (46.5 $\mu g/m^3$); Harriman, TN (32.5 $\mu g/m^3$); St. Louis, MO (31.4 $\mu g/m^3$); Topeka, KS (26.4 $\mu g/m^3$); Watertown, MA (24.2 $\mu g/m^3$); and Portage, WI (18.2 $\mu g/m^3$).

The lowest annual mean $PM_{10}$ concentrations listed in AIRS (1995) were all below 10 $\mu g/m^3$. Examples of areas where annual mean concentrations this low were found include: Campbell Co., WY; Pima Co., AZ; Rosebud Co., MT; and Washington Co., ME. There was interannual variability in concentrations in these areas which sometimes resulted in annual averages greater than 10 $\mu g/m^3$ during the period from 1990 to 1994. At rural sites in national parks, wilderness areas, and national monuments, the annual average $PM_{10}$ concentrations in the western United States during 1988 to 1991 were in the range of 5 $\mu g/m^3$ to 10 $\mu g/m^3$. Higher $PM_{10}$ concentrations have been reported at some rural sites in the eastern United States. The corresponding $PM_{2.5}$ concentrations in western rural or remote sites were approximately 3 $\mu g/m^3$ and in eastern rural or remote sites were in the range of 5 $\mu g/m^3$ to 10 $\mu g/m^3$.

A few attempts to infer various types of "background" levels of $PM_{2.5}$ and $PM_{10}$ have been made. The background levels most relevant to the present criteria document include a "natural background" which excludes all anthropogenic sources anywhere in the world, and a "background" which excludes anthropogenic sources in North America, but not elsewhere. Annual average natural background levels of $PM_{10}$ have been estimated to range from 4 to 8 $\mu g/m^3$ in the western United States and 5 to 11 $\mu g/m^3$ in the eastern United States. Corresponding $PM_{2.5}$ levels have been estimated to range from 1 to 4 $\mu g/m^3$ in the western United States and from 2 to 5 $\mu g/m^3$ in the eastern United States. Twenty-four hour average concentrations may be substantially higher than the annual or seasonal average background concentrations presented in Chapter 6.

***Fine and Coarse Particulate Matter Trends and Patterns***

There are a few sites where information on both fine and coarse PM is available over extended time periods. Most of these data were obtained with dichotomous samplers which measure $PM_{2.5}$ and $PM_{10-2.5}$ (i.e., the coarse fraction of $PM_{10}$). Note that $PM_{2.5}$ will contain some coarse-mode particles as indicated earlier.

Examples were provided in Chapter 6 (Section 10) of $PM_{2.5}$ (fine), the coarse fraction of $PM_{10}$ (coarse), and $PM_{10}$ yearly arithmetic means and $90^{th}$ percentiles and, where daily data were available, daily or every $6^{th}$ day values for one year. Sources used are EPA's Aerometric Information Retrieval System, California Air Resources Board data, the Harvard Six-City data base, and the Harvard Philadelphia data base.

The Harvard Six-City Study provided data during 1980 to 1986. In the dirtier cities, Steubenville, St. Louis, and Harrison, there were decreases in all PM indicators, especially in the earlier years. There was also an apparent decrease in Topeka, one of the cleaner cities. No trend could be discerned in Watertown or Portage. It was difficult to determine whether there was a greater trend in fine or coarse particles.

AIRS provided some data on fine and coarse PM from 1989 to 1994. No significant trends were evident in $PM_{2.5}$ or $PM_{10-2.5}$ either in the means or the 90th percentile values. $PM_{10}$ and $PM_{10-2.5}$ at the dirtier site in New York City appeared to have decreased from 1988 to 1992 but to have increased between 1992 and 1994. Other data from a number of sites in California from 1989 to 1995 also showed very slight downward trends for both fine and coarse PM. The California sites, however, showed substantial seasonal variability in both fine and coarse-mode particle concentrations.

Several data sets from Philadelphia were combined to show TSP trends from 1973 to 1990 and changes in fine and coarse PM from the 1980 period to the 1990 period. TSP came down rapidly between 1973 and 1981 and leveled off thereafter. Fine particle concentrations were approximately 30% higher in the 1980-1982 period than in the 1992-1993 period.

The data base of fine and coarse PM allowed an analysis of the fractions of $PM_{10}$ due to both fine and coarse PM. The annual ratios of $PM_{2.5}$ to $PM_{10}$ were within the range of 0.5 to 0.6 for most eastern U.S. urban stations, but there was considerable spatial and seasonal variability. In Philadelphia, the fine fraction of PM was fairly stable over the year.

During the 1993-1994 period, the mean $PM_{2.5}/PM_{10}$ ratio was 0.71, with a coefficient of variation (CV) of 18%. In contrast, the fine fraction of $PM_{10}$ was seasonally quite variable in California, in general being higher in the winter and lower in the summer. For example, a mean ratio of 0.50 and CV of 26% was found in Azusa, a mean ratio of 0.44 and CV of 43% in Bakersfield, and a mean of 0.29 and CV of 34% for El Centro. This illustrates limitations in trying to infer $PM_{2.5}$ concentrations from $PM_{10}$ or TSP measurements unless site-specific ratios are available. The ratio of $PM_{2.5}$ to $PM_{10}$ values may vary substantially from location to location or from one season to another at the same site.

***Day-to-Day Variability of PM Concentrations***

The only data set from which the daily variability in $PM_{2.5}$ and $PM_{10}$ concentrations could be assessed, based on daily measurements, was obtained in Philadelphia, PA from 1992 to 1995. Average day-to-day concentration differences obtained were 6.8±6.5 $\mu g/m^3$ for $PM_{2.5}$ and 8.6±7.5 $\mu g/m^3$ for $PM_{10}$. Maximum day-to-day differences obtained were 54.7 $\mu g/m^3$ for $PM_{2.5}$ and 50.4 $\mu g/m^3$ for $PM_{10}$.

## 13.2.7 Community and Personal Exposure Relationships

As discussed in Chapters 6 and 7, atmospheric behavior differences between fine-mode and coarse-mode particles lead to important differences in relationships between personal exposure and ambient concentrations measured at a central fixed-site monitor. Fine particles tend to have long atmospheric half-lives, can travel long distances, and therefore can result from distant or widely distributed sources. Evidence from one eastern city, Philadelphia, suggests that the concentrations of fine particles may be uniform over that urban area. Therefore, a measurement at one site may give a reasonable estimate of the fine particle concentration across a city or even wider regional areas, assuming the site is not unduly influenced by a local source of fine particles. Coarse particles, however, have more localized and variable sources and because such particles are rapidly removed, their concentration decreases with distance from the source and the distribution may not be uniform across a city or region. Thus, people in one part of a city may experience high concentrations of coarse fraction particles on one day while people in a different part of the city may experience high concentrations on another day, even though the city-wide average

concentration may be the same on both days. This unevenness of coarse mode particles across a city may need to be taken into account when assessing health impacts in community epidemiological studies.

A further consideration arises with regard to relationships between ambient (outdoor) PM concentrations and personal or indoor exposures. Because people spend most of their time indoors, the particle concentrations indoors tend to dominate personal exposures. However, indoor exposure is due both to particles generated indoors and to ambient particles generated outdoors but which have infiltrated indoors. Major indoor sources of fine particles are smoking and cooking. The major indoor sources of coarse particles are indoor activities that resuspend previously settled PM and that stir up and suspend other materials, including a variety of biological materials such as mold spores and insect debris. Household cleaning, especially dusting and vacuuming, can dramatically increase coarse particle concentrations. When doors and windows are open, both fine-mode and coarse-mode particles will penetrate from outdoors to indoors. When doors and windows are closed, particle penetration might be expected to be dependent on size and air exchange rate, but two experimental studies (Thatcher and Layton, 1995; Koutrakis et al., 1993) suggest that particle penetration may be independent of particle size up to about 10 $\mu$m $d_{ae}$. Once indoors, however, particle size becomes important. Coarse-mode particles are rapidly removed by deposition, whereas accumulation-mode particles have longer half-lives. The production of indoor-generated particles is controlled by daily indoor activities. Therefore, the exposure to indoor-generated particles will not be correlated with the concentration of ambient (outdoor-generated) particles, and time-series epidemiology based on ambient measurements are unlikely to identify health effects related to indoor-generated particles.

The various penetration and removal processes can be modeled, and the equilibrium ratio of the concentration of ambient particles which have penetrated indoors and remained suspended to the concentration of ambient particles outdoors (called the infiltration ratio) can be calculated as a function of the air exchange rate, the penetration factor (assumed to be 1.0 for PM < 10 $\mu$m), and the removal rates which are a function of particle size. Infiltration ratio calculations, based on data from the Particle Total Exposure Assessment Methodology Study (PTEAM), reviewed in Chapter 7, are graphically depicted in Figure 13-2. As is evident, the infiltration ratio of sulfate, which is almost completely of outdoor origin and

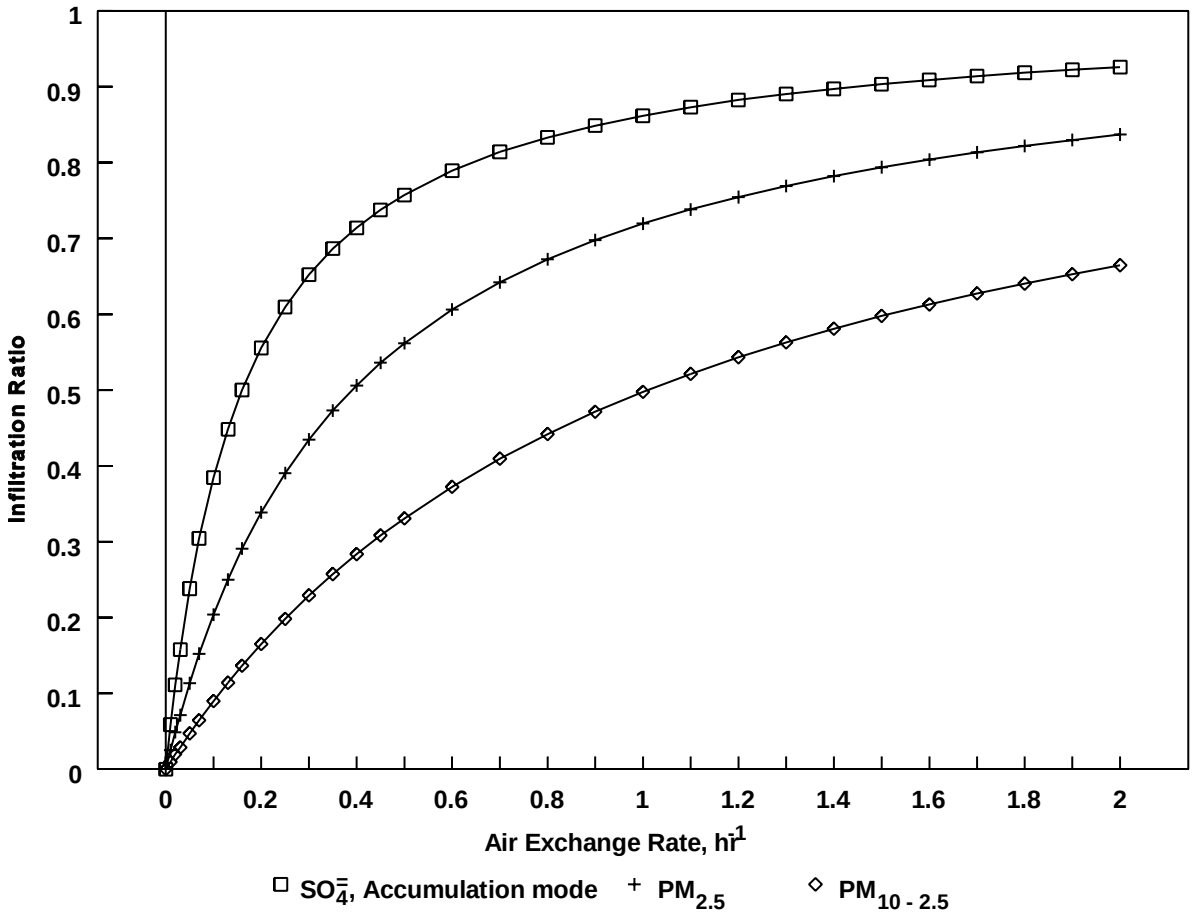


**Figure 13-2. Ratio of indoor concentration of ambient PM to outdoor concentration (infiltration ratio) for sulfate (an indicator of accumulation-mode particles), $PM_{2.5}$, and the coarse fraction of $PM_{10}$ ($PM_{10-2.5}$), as a function of air exchange rate. Based on data from PTEAM.**

expected to be in the fine-mode, is greater than that of $PM_{2.5}$, which may contain some coarse-mode material from both indoor and outdoor sources and thus have a larger effective $d_{ae}$ than sulfate. $PM_{2.5}$ in turn has a greater infiltration ratio than $PM_{10-2.5}$.

The more uniform distribution of ambient fine-mode particles across a city and the higher infiltration ratio for fine particles, means that an ambient measure of fine particles at a central site may provide a useful estimate of the average exposure of people in the community to ambient fine-mode particles. For example, experimental data on personal exposure to sulfate, which are predominantly of outdoor origin and in the fine-mode particle size range, show consistently high correlation of total human exposure to sulfate with outdoor central-site

measurements of ambient sulfates ($0.78 < R^2 < 0.92$) (Suh et al., 1993). However, because of the non-uniform regional concentrations and lower infiltration ratios, an ambient measure of coarse particles at a central site may not provide nearly as good an indication of exposure of people in the community to ambient coarse particles. Much of the time-series epidemiology currently available is based on ambient TSP or $PM_{10}$ measurements, which represent the sum of fine and coarse (in the case of TSP) or the sum of fine particles and the coarse-mode fraction of $PM_{10}$ (in the case of $PM_{10}$). In Philadelphia, and to a lesser extent some other cities (where $PM_{10}$ is not dominated by coarse wind-blown dust), it has been shown that TSP and $PM_{10}$ concentrations correlate better with $PM_{2.5}$ concentrations than with the coarse fraction of $PM_{10}$. It is thus possible that the observed statistical relationships between various ambient particle indicators and health outcomes are largely due to an underlying relationship between fine-mode particles and health outcomes. This hypothesis is supported by recent epidemiological analyses for cities where both $PM_{2.5}$ and $PM_{10-2.5}$ data are available (Schwartz et al., 1996a).

## 13.3 CONSIDERATION OF FACTORS AFFECTING DOSIMETRY

Because the tissue dose of a putative toxic moiety is not always proportional to the ambient exposure of a compound and because the response is more likely related to the tissue dose, contemporary health risk assessment emphasizes the need to clearly distinguish between exposure concentration and internal doses to critical target tissues. The term "exposure-dose-response" assessment has been recommended as more accurate and comprehensive (Andersen et al., 1992). Characterization of the exposure-dose-response continuum is advocated as a way to reduce the uncertainty in extrapolations required from laboratory animal data or from typical humans to susceptible members of the human population. In the case of PM, such characterization requires the elucidation and understanding of the mechanistic determinants of particle deposition and clearance, toxicant-target interactions, and tissue responses.

### 13.3.1 Factors Determining Deposition and Clearance

Particles are deposited in the respiratory tract by mechanisms of impaction, sedimentation, interception, diffusion, and electrostatic precipitation. Differences in ventilation rates, in the upper respiratory tract structure, and in the size and branching pattern of the lower respiratory

tract between species and among humans of different ages and disease states result in significantly different patterns of particle deposition due to the effects of these geometric variations on air flow patterns. The relative contribution of each deposition mechanism to the fraction of particles deposited varies for each region of the respiratory tract (extrathoracic, ET; tracheobronchial, TB; and alveolar, A). Air flow in the ET region is characterized by high velocity and abrupt directional changes, so that the predominant deposition mechanism in this region is inertial impaction. Although, for ultrafine particles, the dominant mechanism in the ET region is diffusion. In the A region, diffusional deposition is also important since many smaller particles penetrate to this region.

Disposition and retention of initially deposited particles depends on clearance and translocation mechanisms that also vary with each region of the respiratory tract. Sneezing and nose wiping or blowing and mucociliary transport to the gastrointestinal tract via the pharynx are important clearance processes for particles deposited in the ET region, whereas coughing, mucociliary transport, endocytosis by macrophages or epithelial cells and dissolution and absorption into the blood or lymph are important in the TB region. Smoking reduces the rate of respiratory tract clearance. Endocytosis by macrophages or epithelial cells and dissolution and absorption into the blood or lymph are the dominant mechanisms in the alveolar region. Depending on their solubility, particles deposited in the alveolar region could have long residence times. The ultimate disposition and retention of a deposited dose is thus dependent on the initial site of deposition, physicochemical properties of the particles (e.g., solubility), and on time since deposition.

The influence of different airway geometry on airflow patterns and subsequent deposition have been documented both empirically and with theoretical modeling. Simulations discussed in Chapter 10 suggest deposition differences among children and adults, with adolescents (age 14 to 18) predicted to have greater respiratory tract daily mass deposition ($\mu$g/d) of submicron particles than adults. Changes in respiratory tract architecture, especially in the smaller conducting airways and gas exchange regions, can be critical factors affecting the dosimetry of inhaled particles. Ambient particles will be deposited in the lung to varying degrees depending on their aerodynamic and physicochemical properties. Changes in architecture or geometry of the respiratory tract

with disease affect airflow and thereby the aerodynamic behavior of inhaled particles. A mismatch of ventilation and perfusion in lung diseases, such as emphysema, chronic obstructive pulmonary disease (COPD), and asthma has been noted (Bates et al., 1971; Bates, 1989). Chronic bronchitis, emphysema, and chronic airways obstruction all fall within the aegis of COPD, and both it and asthma result in altered airflow. In more severe stages of these diseases, the healthy portion of the lung receives more of the tidal volume which can result in some ventilatory units receiving an increased particle burden compared to others. Kim et al. (1988) demonstrated greater particle deposition, using an aerosol rebreathing test, in COPD patients versus healthy subjects. The increase in deposition correlated with the degree of airway obstruction. Anderson et al. (1990) also showed that the deposition of ultrafine particles in patients with COPD is greater than in healthy subjects. Svartengren et al. (1994) showed enhanced deposition in asthmatics. Bennett et al. (1996) reported a greater deposition rate (particles/time) in COPD patients relative to healthy subjects and that these patients under resting breathing conditions receive an increasing dose of inhaled fine particles with increased severity of their airways disease. Model simulations discussed in Chapter 10 predict that dose expressed in terms of numbers of particles per anatomical unit would be increased in individuals with compromised lungs relative to healthy subjects (Miller et al., 1995).

Not only may patients with preexisting COPD be susceptible because of an enhanced or altered deposited dose pattern, but their disease may also predispose these patients to altered responses to the toxic effects of ambient PM (discussed in the next section). To the extent that cigarette smoke contributes to changes in architecture and response, smokers can also be considered a potentially susceptible population for the effects of PM.

Physicochemical characteristics of particles (e.g., particle diameter, distribution, hygroscopicity) interact with the anatomic (e.g., branching pattern) and physiologic (e.g., ventilation rate, clearance processes) factors to influence deposition and retention of inhaled aerosols. For a given aerosol, the two most important parameters which characterize size distribution, and hence deposition, are the MMAD and the $\sigma_g$ of the particles. It must be emphasized that the relative contribution of these anatomic, physiologic, and physicochemical determinants is a dynamic relationship. Further, the relative contribution of these determinants is also influenced by exposure conditions such as concentration and duration.

The influence of the particle size distribution on the fraction of particles deposited in the respiratory tract is illustrated in Figure 13-3. This figure depicts the predicted deposition fractions for an adult male, using a general population ventilation activity pattern, in the alveolar (A), tracheobronchial (TB), and thoracic (A + TB) regions. The difference between total respiratory tract and total thoracic deposition fractions represents the extrathoracic (ET) or upper airway deposition fraction. The deposition fraction in the respiratory tract, relative to unit mass concentration in air, is shown for particles of different MMAD, in the range of 0.1 to 100 $\mu$m, for two different geometric standard deviations ($\sigma_g$ = 1.8 in the top panel and $\sigma_g$ = 2.4 in the bottom panel).

These simulations show that alveolar deposition fraction is fairly uniform for aerosols between 0.5 and 4.0 $\mu$m MMAD. Deposition fraction of particles in the A region increases for particles less than 0.5 $\mu$m because diffusion becomes the dominant mechanism. In the aerodynamic range of particles ($\geq$ 1.0 $\mu$m MMAD), deposition fraction increases as particle size increases and sedimentation and impaction become important deposition mechanisms, especially for the larger particles (> 5 $\mu$m MMAD) in the TB region. This pattern is altered slightly for mouth breathing versus normal breathing, in that mouth breathers have a greater TB deposition of particles greater than 2.5 $\mu$m (i.e., the coarse fraction of $PM_{10}$) than they would if breathing PM only via the nose. The pattern is also influenced by the degree of dispersion of the particle sizes. Polydispersity decreases the deposition fraction of particles in the aerodynamic range as shown by decrements in the bottom panel for the polydisperse aerosol ($\sigma_g$ = 2.4) compared to the more monodisperse aerosol ($\sigma_g$ = 1.8) in the top panel.

The collection fraction for $PM_{10}$ and $PM_{2.5}$ samplers are also depicted in Figure 13-3. As considered for the basis of the previous PM standard, the $PM_{10}$ sampler collection curve shows that this sample accounts well for thoracic (TB + A) deposition but excludes many of the larger particles which would be deposited in the ET region. Also, the $PM_{2.5}$ cutpoint does not capture some larger particles that would be deposited in the TB and A regions, especially in mouth breathers under the simulated conditions. These simulations corroborate that the 10 $\mu$m cut point is appropriate to separate ambient particles that have the potential to deposit in the lower respiratory tract versus those in ET regions. However, these results also

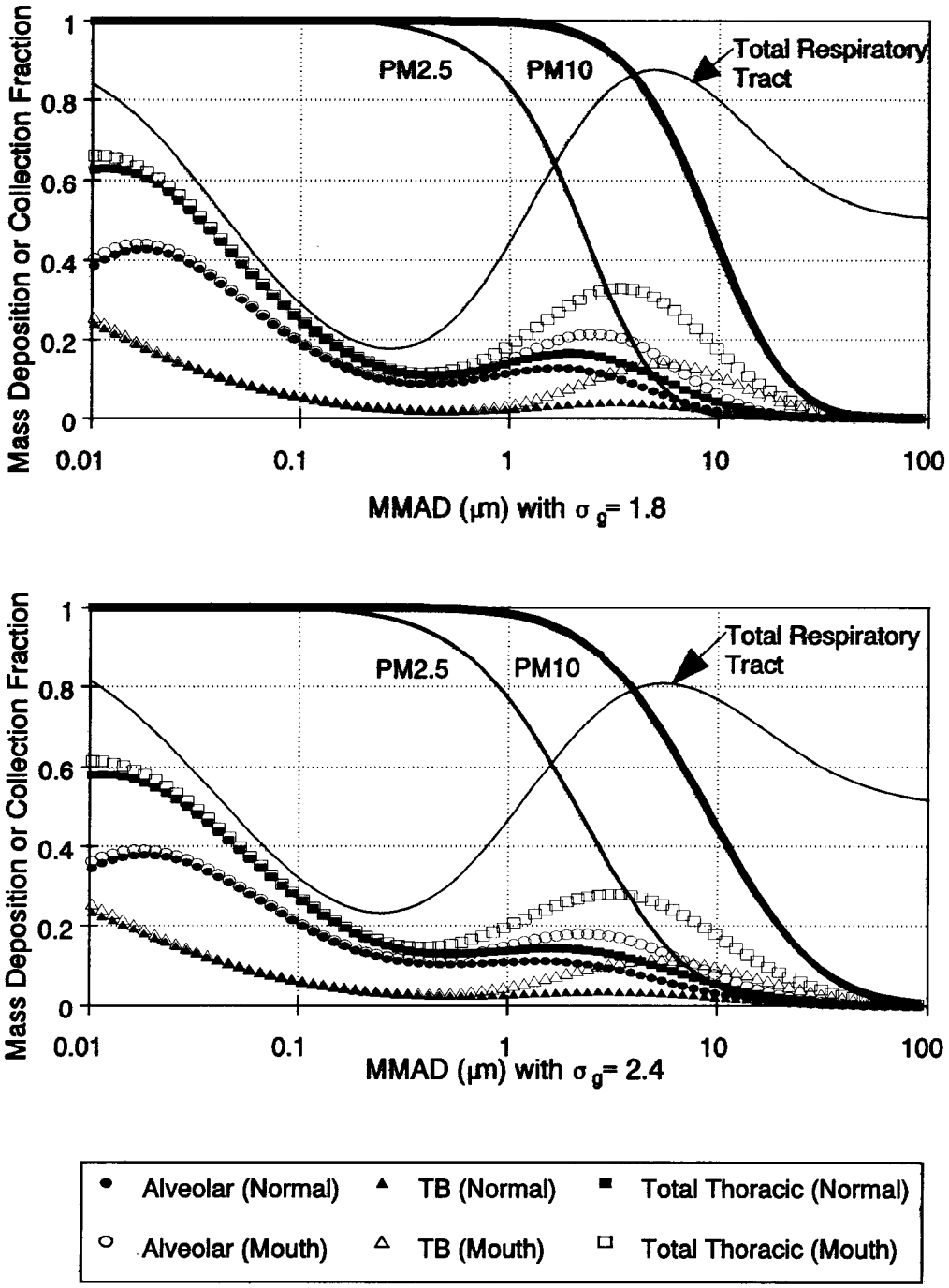


**Figure 13-3. Human respiratory tract PM deposition fraction and $PM_{10}$ or $PM_{2.5}$ sampler collection versus mass median aerodynamic diameter (MMAD) with two different geometric standard deviations ($\sigma_g$ = 1.8 or $\sigma_g$ = 2.4). Alveolar, tracheobronchial, or total thoracic deposition fractions predicted for normal augmenter versus mouth breather adult male using a general population (ICRP66) minute volume activity pattern and the 1994 ICRP66 model.**

suggest that an intermediate cut point that is directly comparable to separation of fine- and coarse-mode particles is not supported on the basis of considering particle deposition alone, due to the fact that particles in the coarse fraction of $PM_{10}$ also have some efficiency for deposition in both the A and TB regions. As discussed previously, construction of the exposure-dose-response continuum is also dependent on defining a dose metric that is relevant to the mechanism of action for a compound.

### 13.3.2 Factors Determining Toxicant-target Interactions and Response

Differences in susceptibility can be due to factors influencing deposited and retained particle mass or number, toxicant-target interaction, or tissue sensitivity (e.g., conditions causing altered or enhanced target tissue response). Discussion of various individual risk factors that might influence tissue response to a delivered dose is provided in Section 13.6. Since the target tissue has been identified as the lower respiratory tract, however, some generalizations for the definition of dose can be useful in trying to ascertain if one metric may be more appropriate than another to describe a given toxicant-target interaction.

The biologically-effective dose resulting from inhalation of particles can be defined as the time integral of total inhaled particle mass, particle number, or particle surface area per unit of respiratory tract surface area or per unit mass of the respiratory tract. Choice of the metric to characterize the biologically-effective dose should be motivated by insight into the mechanisms of action of the compound (or particles) in question. The biologically-effective dose may be accurately described by particle mass or number deposition alone if the particles exert their primary action on the surface contacted (Dahl et al., 1991). For longer-term effects, the deposited dose may not be a decisive metric, since particles clear at varying rates from the different respiratory tract regions. When considering the epidemiologic data, dose metrics could be separated into two major categories, pattern and quantity of acute deposition and the pattern and quantity of retained dose. The deposited dose may be more important for daily mortality, hospital admissions, work loss days, etc. On the other hand the retained dose may be more important for chronic responses such as induction of chronic disease, shortening of life-span ("premature" mortality), or diminished quality of life although repeated acute responses may also be related to chronic responses.

To date, most analyses have relied upon the particle mass concentration ($\mu g/m^3$) breathed by exposed individuals. If relative risk (RR) estimates were calculated based on various internal dose metrics (e.g., deposited dose [mass] normalized per unit tracheobronchial or alveolar surface area or normalized per critical cell type such as the alveolar macrophage), some of these relationships could change or be modified. Moreover, not only is there a question about how the doses should be normalized (e.g., by body mass, lung epithelial surface area, etc.), but also as to whether the PM dose should be expressed as numbers of particles, aggregate particle surface area, or total particle mass in a given size fraction. The fine fraction contains by far the largest number of particles, and those particles generally have a larger aggregate surface area than coarse-mode particles. Such considerations may be important when trying to ascertain the appropriate dose metric for evaluation of lower respiratory tract health outcomes. For example, retardation of alveolar macrophage phagocytosis due to particle overload appears to be better correlated with particle surface area than particle mass (Morrow, 1988; Oberdörster et al., 1995a,b). Also, ultrafine particles have been shown to be less effectively phagocytosed by macrophages than larger particles (Oberdörster et al., 1992a,b).

Figure 13-4 presents an example which illustrates the complexities of considering PM "dose" using different metrics (e.g., such as mass, surface area, and number of particles) that are typical for a Southern California urban aerosol (Whitby, 1978). For the accumulation mode, which constitutes about 40% of the total mass in the illustrated sample, the geometric mean for the volume distribution, DGV, equivalent to the volume median diameter, is 0.31 $\mu$m. When the median diameter is expressed in terms of surface area, or count, the respective median diameters of the fine mode are 0.19 $\mu$m and 0.07 $\mu$m. By far the largest number of particles are contained in the nuclei mode, which is inconsequential in terms of mass. It must be remembered that the composition of the particles in each mode is different as are their hygroscopicity, solubility, translocation pathways, and toxicity.

Table 13-2 shows the predicted deposition efficiency in various regions of the respiratory tract for the aerosol depicted in Figure 13-4, which illustrates different particle diameters and size distributions that are typical of the nuclei, accumulation, and coarse modes of ambient particles. These are predicted from simulations as performed in

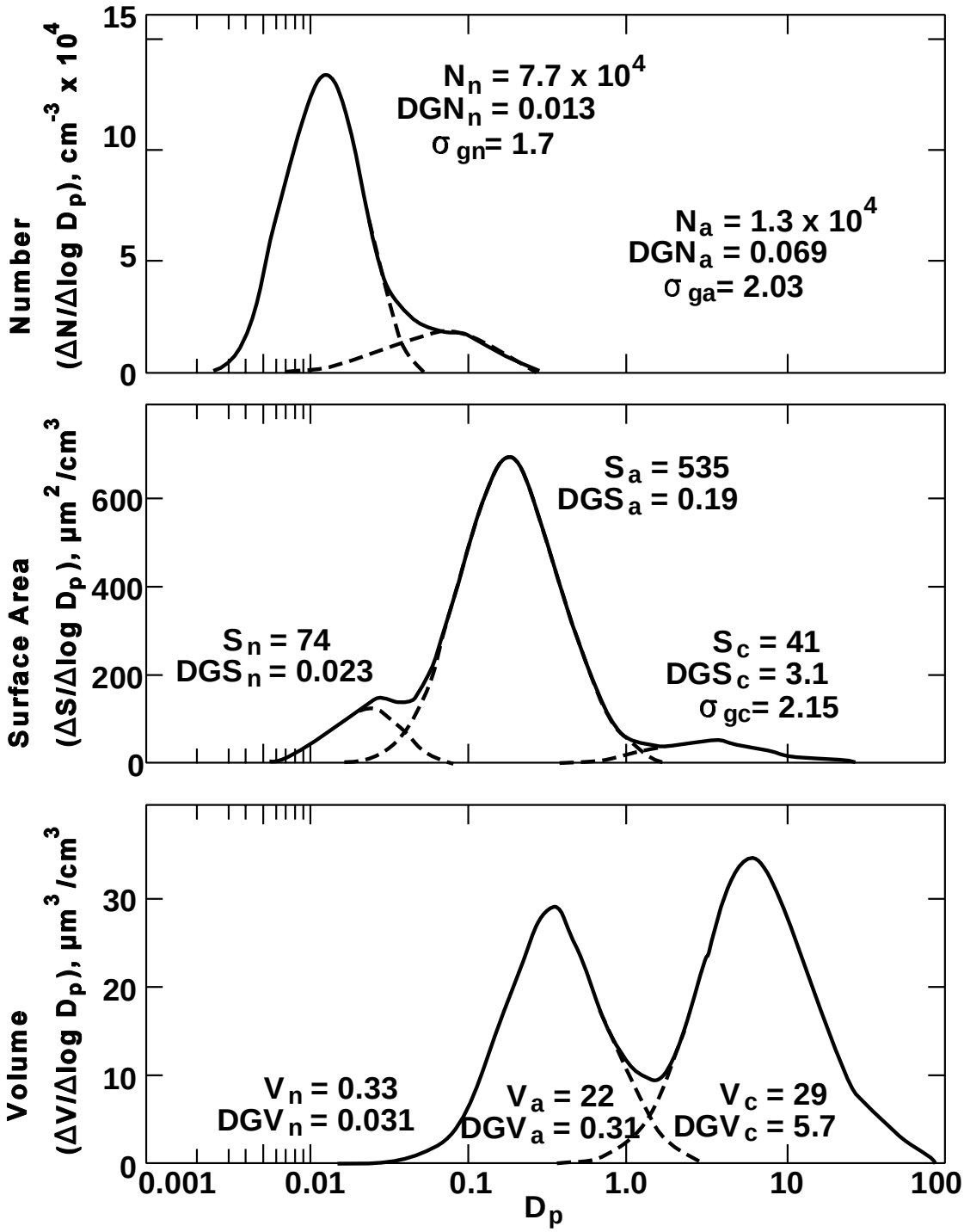


**Figure 13-4. Distribution of coarse (c), accumulation (a), and nuclei or ultrafine (n), mode particles by three characteristics, volume (V), surface area (S), and number (N). DVG = geometric mean diameter by volume; DGS = geometric mean diameter by surface area; DGN = geometric mean diameter by number; $D_p$ = geometric diameter.**

Source: Whitby (1978).

**TABLE 13-2. PREDICTED RESPIRATORY TRACT DEPOSITION AS A PERCENTAGE OF TOTAL INHALED MASS FOR THE THREE PARTICLE SIZE MODES IN THE AEROSOL DEPICTED IN FIGURE 13-4**

| | MMAD = 0.029 $\mu$m | MMAD = 0.27 $\mu$m | MMAD = 6.9 $\mu$m |
|---|---|---|---|
| | $\sigma_g$ = 1.7 | $\sigma_g$ = 2.03 | $\sigma_g$ = 2.15 |
| | $\rho$ = 1.4 g cm$^{-3}$ | $\rho$ = 1.2 g cm$^{-3}$ | $\rho$ = 2.2 g cm$^{-3}$ |
| Deposition Site | Nuclei Mode | Accumulation Mode | Coarse Mode |
| Extrathoracic Region | 0.05 | 1.8 | 52.5 |
| Tracheobronchial Region | 0.07 | 0.8 | 2.1 |
| Alveolar Region | 0.02 | 2.8 | 3.4 |
| Exhaled | 0.02 | 23.8 | 12.4 |

[a]Dynamic shape factor (used to calculate MMAD from measured MMD) assumed for all three particle size modes to be 1.5 (ICRP, 1994).
MMD = mass median diameter (equivalent geometric).
MMAD = mass median aerodynamic diameter.
$\sigma_g$ = geometric standard deviation.
$\rho$ = particle density.

Chapter 10 for the aerosols of Phoenix, AZ and Philadelphia, PA. The patterns are different for the different modes.

How could particle size be important in biological activity? The mass of the particle may be important if the mechanism of action of the particle is related to its persistence. For example, large acid droplets require a much longer time to undergo neutralization than very small droplets and therefore would be more likely to reach intrathoracic airways as acid rather than as a neutralization product. Larger particles will take longer to dissolve or to be degraded enzymatically. If presentation of active groups to cell surfaces is important in the mechanisms of action, then the total surface area of the particles may be important. The largest aggregate surface area is contained in the accumulation mode. The particle mode with the largest surface area will be able to present the largest number of reactive surface groups to the cell surface. This feature would presumably be most important for relatively less soluble particles. Biological effects on epithelial cells or macrophages may depend on

the number of cell surface receptors that are stimulated or occupied. The number of particles may be related to their toxic effect. For example, if the number of separate phagocytotic events determines the capacity of a cell to ingest particles, then number becomes important. Numbers may also be important with regard to particles interacting with surface receptors of epithelial or phagocytic cells.

### 13.3.3 Construction of Exposure-Dose-Response Continuum for PM

It is clear that the characterization of the exposure-dose-response continuum from PM exposure data to human morbidity/mortality risk is far from complete. As defined by the National Research Council Board on Environmental Studies and Toxicology, a "biologic marker" is any cellular or molecular indicator of toxic exposure, of an adverse health effect, or of susceptibility (National Research Council, 1987). The markers represent signals — generally biochemical, molecular, genetic, immunologic, symptomatic (e.g., cough), or physiologic — in a continuum of events between a causal exposure and resultant disease.

The events in the progression from exposure to disease are not necessarily discrete, nor the only events in the continuum, and represent a conceptual temporal sequence. The paradigm of a continuum is only meant to illustrate a single pathway among many pathways to a biologic endpoint from a given exposure. Whether the progression is exactly linear or some other form, such as a multidimensional network, is debatable (Schulte, 1989). In most exposure-disease relationships, the linear causal sequence is an implied framework for research purposes. Appraisal of the validity of the components of the sequence requires that the framework be made explicit and that the existence of causal relationships be tested. That is, to better model the situation, one would consider that there may be multiple pathways leading to a given disease outcome. This is especially true for the etiology of most ambient air pollution-related biomedical outcomes. The effect of interest is often small in comparison to effects of other etiologic factors, and exposure itself may be confounded with that to other compounds and by inadequate characterization of temporal relationships.

Many advances in the understanding and quantification of the mechanistic determinants of toxicant-target interactions and tissue responses (including species sensitivity) are required before an overall model of a pathogenesis continuum can be constructed for ambient air PM. As our understanding is supplemented by identification of intervening relationships and components

are characterized more precisely or with greater detail, health events are less likely to be viewed as dichotomous (e.g., death or not; presence or absence of disease) but rather as a series of changes in a continuum from homeostatic adaptation, through dysfunction, to disease and death. The critical effect could become that biologic marker deemed most pathognomonic or of prognostic significance, based on a validated hypothesis of the role of the marker in the development of disease. As more causal component linkages are identified, it becomes more possible to elucidate quantitative relationships of the kinetics, natural history, and rates of transition along the continuum. Multiple markers may be more efficacious than a single marker for characterizing any given component.

Supplementary independent studies (typically toxicological), required to establish the validity of postulated intermediate components (markers) between exposure and disease, relevant to the observed mortality and morbidity in PM epidemiologic investigations, have been encumbered by methodologic difficulties. For example, differences in dosimetry due to altered flow patterns caused by geometric variation of the respiratory tract in different species have important implications for interspecies extrapolation. Toxicological data in laboratory animals typically can aid the interpretation of human clinical and epidemiological data because they provide concentration- and duration-response information on a more complex array of effects and exposures than can be evaluated in humans. However the use of laboratory animal toxicological data has typically been limited because of difficulties in quantitative extrapolation to humans. The various species used in inhalation toxicological studies do not receive identical doses in comparable respiratory tract regions (ET, TB, A) when exposed to the same aerosol (same composition, mass, concentration, and size characteristics). Such interspecies differences are important because the adverse toxic effect is likely related more to the quantitative pattern of deposition within the respiratory tract than to the exposure alone; this pattern determines not only the initial respiratory tract tissue dose, but also the specific pathways by which the inhaled particles are cleared and redistributed. Until these differences can be quantified, these dosimetric interspecies differences will impede characterization of the exposure-dose-response continuum for PM components and mixtures.

Another difficulty in elucidating the exposure-dose-response continuum using laboratory animal data is that different endpoints are typically assayed in the laboratory animals and the

relationship of these endpoints to the human health outcomes of interest have not been established. For example, the epidemiological studies evaluate endpoints such as illness, hospital admissions, and emergency room/doctor visits whereas the homologous biochemical or pathological endpoints in the laboratory animal models are unknown. Although the ultimate goal, for example, may be to estimate the responses of elderly persons with cardiopulmonary disease, most laboratory animal studies are normally performed on homogeneous populations of healthy animals and the majority of human clinical studies are performed on healthy young subjects or those with only mild disease.

In summary, until the mechanism(s) of action for effects induced by ambient PM or its important constituents can be characterized, the linkage between exposure and response provided by dosimetry will remain weak and only qualitative at best. Until dose metrics can be defined that correlate well with PM mechanism(s) of action, insights from dosimetry will be limited. Clearly, inhaled dose is important, but the best exposure/dose metric(s) to relate quantitatively to acute or chronic health outcomes awaits elucidation of pertinent mechanisms. Should the dose be normalized to regional surface area, for example, or expressed relative to some other critical mechanistic determinant (e.g., possibly per alveolar macrophage)? Once pertinent mechanism(s) of action are delineated, different biomedical indices can be used to characterize intermediate linkages to mortality or morbidity outcomes and to quantify relationships across the exposure-dose-response continuum. Towards that ultimate objective, both improved epidemiologic studies, using more refined measures of PM exposure (e.g., for fine versus coarse mode fractions of $PM_{10}$, for ultrafine particles, for particle number concentration, or for various classes of chemical constituents) and more laboratory animal studies evaluating effects of real-world concentrations of ambient PM mixtures or constituents are needed.

## 13.4 HEALTH EFFECTS OF PARTICULATE MATTER

This section evaluates available scientific evidence regarding the health and physiologic effects of exposure to ambient PM. The main objectives of this evaluation are as follows: (1) to summarize and evaluate the strengths and limitations of available epidemiologic findings; (2) to assess the biomedical coherence of findings across studied endpoints and

scientific disciplines; (3) to evaluate the plausibility of available evidence in light of mechanistic, pathophysiologic, and dosimetric considerations; and (4) to assess the extent to which observed effects can be attributed to PM and to specific size fractions and chemical constituents within the PM complex. Epidemiologic findings are emphasized first because they provide the largest body of evidence directly relating ambient PM concentrations to biomedical outcomes.

By far the strongest evidence for ambient PM exposure health risks is derived from epidemiologic studies. Many epidemiologic studies have shown statistically significant associations of ambient PM levels with a variety of human health endpoints, including mortality, hospital admissions and emergency room visits, respiratory illness and symptoms measured in community surveys, and physiologic changes in mechanical pulmonary function. Associations of both short-term and long-term PM exposure with most of these endpoints have been consistently observed. The general internal consistency of the epidemiologic data base and available findings have led to increasing public health concern, due to the severity of several studied endpoints and the frequent demonstration of associations of health and physiologic effects with ambient PM levels at or below the current U.S. NAAQS for $PM_{10}$. The weight of epidemiologic evidence suggests that ambient PM exposure has affected the public health of U.S. populations. However, there remains much uncertainty in the published data base regarding the shapes of PM exposure-response relationships, the magnitudes and variabilities of risk estimates for PM, the ability to attribute observed health effects to specific PM constituents, the time intervals over which PM health effects are manifested, the extent to which findings in one location can be generalized to other locations, and the nature and magnitude of the overall public health risk imposed by ambient PM exposure.

The etiology of most air pollution-related health outcomes is highly multifactorial, and the effect of ambient air pollution exposure on these outcomes is often small in comparison to that of other etiologic factors (e.g., smoking). Also, ambient PM exposure in the U.S. is usually accompanied by exposure to many other pollutants, and PM itself is composed of numerous physical and chemical components. Assessment of the health effects attributable to PM and its constituents within an already-subtle total air pollution effect is difficult even with well-designed studies. Indeed, statistical partitioning of separate pollutant effects may

somewhat artificially describe the etiology of effects which actually depend on simultaneous exposure to multiple air pollutants. Furthermore, identification of anatomic sites at which particles trigger end-effects and elucidation of biological mechanisms through which these effects may be expressed are still at an early stage. Thus, it remains difficult to form incisive a priori hypotheses to guide epidemiologic and experimental research. Lack of clear mechanistic understanding also increases the difficulty with which available findings can be integrated in assessing the coherence of PM-related evidence.

In this regard, several viewpoints currently exist on how best to interpret the epidemiology data: one sees PM exposure indicators as surrogate measures of complex ambient air pollution mixtures and reported PM-related effects represent those of the overall mixture; another holds that reported PM-related effects are attributable to PM components (per se) of the air pollution mixture and reflect independent PM effects; or PM can be viewed both as a surrogate indicator as well as a specific cause of health effects. In any case, reduction of PM exposure would lead to reductions in the frequency and severity of the PM-associated health effects.

Several other key questions and problems also must be considered when attempting to interpret the data reviewed in this document. While the epidemiology data provide strong support for the associations mentioned above, no credible supporting toxicologic data are yet available that provide insight into potential mechanisms. There is also a paucity of information of either a biological or clinical nature that argues for the biologic plausibility of the epidemiologic results. Nor is there much toxicologic data that elucidates the role of specific PM constituents in mediating responses of the type demonstrated by the epidemiologic analyses at low ambient PM concentrations. More specifically, although several hypotheses are discussed later with regard to possible mechanisms by which ambient PM may exert human health effects, little non-epidemiologic evidence is presently available to support or refute a causal relationship (i.e., to construct an exposure-dose-response continuum) between low ambient concentrations of PM and observed increased mortality or morbidity risks. Thus, specific causal agents cannot presently be confidently identified among typical ambient PM constituents, nor can mechanisms be clearly specified by which health effects of ambient PM are exerted.

Due to these uncertainties much caution is warranted with regard to derivation or extrapolation of quantitative estimates of increased risks for mortality or morbidity related to low level ambient PM exposures based on available epidemiology information.

## 13.4.1 Epidemiologic Evidence for Ambient PM Health Impacts

The health effects of short (24 h) and long-term (annual) PM exposure on mortality, hospitalization, respiratory symptom/illness, and pulmonary function change are examined across epidemiological, laboratory animal and controlled human studies. Where the information is available, the data for these health endpoints are also related to particle size, including $PM_{10}$, $PM_{2.5}$, and $PM_{(10-2.5)}$, as well as to specific chemical constituents such as $SO_4^=$ or $H^+$.

### 13.4.1.1 Ambient PM Mortality Effects

Early epidemiology studies of severe air pollution episodes in Europe and the U.S. from the 1930's to 1950's indicated that exposure to high ambient levels of urban air pollution can produce serious human health effects. By far, the most clearly defined health effects attributable to ambient PM exposure are the marked increases in daily deaths that occurred during episodes of high pollution (e.g., in the Meuse Valley in 1930, in Donora in 1948, and in London in 1952). During a London episode in the 1950s, for example, more than 4,000 excess deaths during a 4 to 5-day period were attributed to air pollution, with the greatest increase in death seen most clearly among patients over 45 years with lung and heart disease. The early episode studies demonstrated, as subsequently confirmed in several re-analyses, that primary and secondary particulate combustion products and sulfur oxide air pollution at sufficiently high concentrations (in excess of 500 to 1,000 $\mu g/m^3$ BS), exert lethal effects even though conclusively substantiated mechanisms of action underlying the observed episodic mortality have yet to be elucidated.

Recent studies in a variety of locations, summarized in Chapter 12, further implicate air pollution exposure in mortality at much lower ambient levels, including levels well below the current 24-h $PM_{10}$ NAAQS of 150 $\mu g/m^3$ and annual $PM_{10}$ NAAQS of 50 $\mu g/m^3$. More than 20 time-series analyses published in the late 1980s and early 1990s demonstrate significant positive associations between daily mortality and 24-h concentrations of ambient

particles indexed by various measures (black smoke, TSP, $PM_{10}$, $PM_{2.5}$, etc.) in numerous U.S. metropolitan areas and in other countries (e.g., Athens, São Paulo, Santiago). These studies collectively suggest that PM alone or in combination with other commonly occurring air pollutants (e.g., $SO_2$) is associated with daily mortality, the effect of PM appearing to be most constituent. In both the historic and recent studies, the association of air pollution exposure with mortality has been strongest in the elderly and for respiratory and cardiovascular causes of death. Furthermore, the recent analyses suggest a major role of PM relative to other air pollutants in terms of increased risk of mortality.

Time-series analyses strongly suggest a positive effect on daily mortality across the entire range of ambient PM levels. Relative risk (RR) estimates for daily mortality in relation to daily ambient PM concentration are consistently positive, and statistically significant (at $P \leq 0.05$), across a variety of statistical modeling approaches and methods of adjustment for effects of relevant covariates such as season, weather, and co-pollutants. Examination of Table 12-4 in Chapter 12 shows that relative risk estimates (RR) for non-accidental mortality in the total population associated with a 50 $\mu g/m^3$ increase in 24-h average $PM_{10}$ range from 1.015 to 1.085. Relative risk estimates with $PM_{10}$ as the only pollutant index in the model range from RR = 1.025 to 1.085, while the $PM_{10}$ RR with multiple pollutants in the model range from 1.015 to 1.025. Higher relative risks are indicated for the elderly and for those with pre-existing respiratory conditions.

Mortality effects associated with chronic, long-term exposure to PM air pollution have been assessed in cross-sectional studies and more recently, in prospective cohort studies. A number of older cross-sectional studies provided indications of increased mortality associated with chronic (annual average) exposures to ambient PM (indexed mainly by TSP or sulfate measurements). However, unresolved questions regarding adequacy of statistical adjustments for other potentially important covariates (e.g., cigarette smoking, economic status, etc.) across cities tended to limit the degree of confidence that could be placed on such studies or on quantitative estimates of PM effects derived from them.

Several more recent studies, in contrast, have used subject-specific information about relevant covariates (such as cigarette smoking, occupational exposure, etc.), and appear to provide more reliable findings of long-term PM exposure effects. In particular, three new prospective cohort studies of mortality associated with chronic PM exposures were evaluated in

Chapter 12 as yielding especially useful information. The studies of California nonsmokers by Abbey et al. (1991) and Abbey (1994) found no significant mortality effects of previous TSP exposure in a small, young cohort. On the other hand, the larger and more extensive Harvard Six Cities (Dockery et al., 1993) and American Cancer Society (ACS) (Pope et al., 1995) studies agree in their findings of statistically significant positive associations between fine particles and excess mortality, although the ACS did not evaluate the contribution of other air pollutants. The RR estimates for total mortality in the Six-Cities study (with their 95 percent confidence intervals) per increments in PM indicator levels are as follows: the RR for 50 $\mu g/m^3$ $PM_{15}$ is 1.42 (1.16, 2.01), the RR for 25 $\mu g/m^3$ $PM_{2.5}$ is 1.31 (1.11, 1.68), and the RR for 15 $\mu g/m^3$ $SO_4$ is 1.46 (1.16, 2.16). The estimates for total mortality derived from the ACS study are 1.17 (1.09, 1.26) for 25 $\mu g/m^3$ $PM_{2.5}$, and 1.10 (1.06, 1.16) for 15 $\mu g/m^3$ $SO_4^=$. In some cases, the life-long cumulative exposure of the study cohorts included distinctly higher past PM exposures, especially in the cities with historically higher PM concentrations; but more current PM measurements were used to estimate the chronic PM exposures. Thus, caution must be exercised regarding the use of the reported quantitative risk estimates, since somewhat lower risk estimates than the published ones are apt to apply. However, the chronic exposure studies, taken together, suggest that there may be increases in mortality in disease categories that are consistent with long-term exposure to airborne particles and that at least some fraction of these deaths reflect cumulative PM impacts above and beyond those exerted by acute exposure events.

The weight of epidemiologic evidence suggests that short-term ambient PM exposure likely contributes to increased daily mortality, and it also suggests that long-term PM exposure reduces survival time. It is extremely unlikely that study designs not yet employed, covariates not yet identified, or statistical techniques not yet developed could wholly negate the large and consistent body of epidemiologic evidence relating short-term PM exposure to daily mortality in U.S. urban areas. Similarly, although relatively few cohort studies of long-term PM exposure and mortality are available, they are consistent in direction and magnitude of excess risk with a larger body of cross-sectional annual mortality studies, and most show positive associations of PM exposure with mortality. In view of the consistency with which they are observed, it is unlikely that these associations could result entirely from important confounding factors as yet unidentified.

Variation in relative risks exists among the estimates for PM-related daily mortality. These estimates would be expected to vary if PM exposure truly affects daily mortality for the following reasons: (1) the toxicity of PM likely depends on its size distribution and chemical composition, and these characteristics differ among geographic areas; (2) local populations differ in demographic and socioeconomic characteristics; (3) the distribution of diseases differs among geographic locations; and (4) ambient PM means and ranges differ among geographic areas. Somewhat different RR estimates are therefore derived across varying PM ranges in different studies, even when they have been standardized to the same PM increment. This results in different site-specific RR estimates, as would be expected unless PM-mortality relationships are truly linear throughout the entire PM range and represent a general non-specific (i.e., chemical composition-independent) PM effect. On balance, the observed variations in RR estimates are not inconsistent with a real effect of PM exposure on daily mortality.

In many studies, daily mortality has been most strongly associated with PM levels occurring shortly (0 to 5 days) before death. These short intervals have been invoked as evidence that PM-induced mortality occurs primarily in persons who would have died soon, even without PM exposure. However, there is no pathophysiologic reason why the exposure-to-death interval need be related to the time by which the death itself is hastened. The existence of short exposure-to-mortality intervals neither requires nor excludes the possibility that at least a portion of PM-associated deaths are advanced by long time intervals. At the same time, available evidence does not allow confident quantitative inference as to PM-associated shortening of life.

***Comparison of Size-Specific and Chemical-Specific Particle Effects on Mortality***

An important objective of this chapter is to evaluate different exposure metrics based on size-specific and chemical-specific information. However, only a limited number of studies have included direct measurements of indicators of fine particle mass (i.e., $PM_{2.5}$, $PM_{2.1}$). Additional indirect support for fine particle effects is derived from studies that used BS, COH, KM, or sulfate measurements, which are primarily associated with components of fine particles. Information on chemical-specific PM constituents is limited to a few studies that included measures of particle strong acidity and/or sulfates; but the results of such analyses may best be

interpreted in terms of the exposure metrics being reflective of fine particle effects in general, rather than of acids or sulfates in particular.

Early indications that fine particles are likely important contributors to observed PM-mortality and morbidity effects came from evaluation of past serious air pollution episodes in Britain and the United States. The most severe episodes, as discussed in the 1982 Criteria Document (U.S. Environmental Protection Agency, 1982), were characterized by several consecutive days of very low wind speed conditions, during which large coarse mode particles rapidly settle out of the atmosphere and concentrations of fine mode particles dramatically increase. Even during non-episode conditions, mortality associations with BS or COH readings in Britain or the U.S. during the 1950s to 1970s most likely reflected contributions of fine mode particles. This is based on the low $D_{50}$ cutpoints ($\approx 4.5$ $\mu$m) for the BS and COH methods described in Chapter 4, although some contribution of small inhalable particles (up to $\sim 10$ $\mu$m) cannot be entirely ruled out.

Table 13-3 summarizes effect estimates (relative risk information) derived from more recent epidemiology studies demonstrating health effects (mortality, morbidity) associations with ambient 24-h $PM_{10}$ concentrations in U.S. and Canadian cities. The evidence summarized in Table 13-3 leaves little doubt that short-term $PM_{10}$ concentrations typical of contemporary U.S. urban air sheds are correlated with detectable increases in risk of human mortality and morbidity. Less extensive evidence summarized in Table 13-4 also suggests that fine particles may be important contributors to the observed PM-health effects associations given the increased risks (of mortality, hospitalization, respiratory symptoms, etc.) associated with several different fine particle indicators (e.g., $PM_{2.5}$, $SO_4^=$, $H^+$).

Because of the potential impact of particle size on their observations, some investigators have attempted to determine what size and/or chemical form of particles had the strongest association with health effects. For example, in initial of data from St. Louis and eastern Tennessee (part of the Six-Cities Study), the strongest associations of daily mortality rates were seen with $PM_{10}$ while progressively weaker associations were seen with $PM_{2.5}$, sulfate, and aerosol acidity (Dockery et al., 1992). However, because of the limited statistical power of the latter study and the lesser quantity of aerosol acidity data (only one year versus seven years for the other PM measures), the observation of weaker association of aerosol acidity with mortality is inconclusive.

**TABLE 13-3. EFFECT ESTIMATES PER 50 $\mu g/m^3$ INCREASE IN 24-h $PM_{10}$ CONCENTRATIONS FROM U.S. AND CANADIAN STUDIES**

| Study Location | RR (± CI) Only PM in Model | RR (± CI) Other Pollutants in Model | Reported $PM_{10}$ Levels Mean (Min/Max)[†] |
|---|---|---|---|
| Increased Total Acute Mortality | | | |
| Six Cities[a] | | — | |
| Portage, WI | 1.04 (0.98, 1.09) | — | 18 (±11.7) |
| Boston, MA | 1.06 (1.04, 1.09) | — | 24 (±12.8) |
| Topeka, KS | 0.98 (0.90, 1.05) | — | 27 (±16.1) |
| St. Louis, MO | 1.03 (1.00, 1.05) | — | 31 (±16.2) |
| Kingston/Knoxville, TN | 1.05 (1.00, 1.09) | — | 32 (±14.5) |
| Steubenville, OH | 1.05 (1.00, 1.08) | — | 46 (±32.3) |
| St. Louis, MO[c] | 1.08 (1.01, 1.12) | 1.06 (0.98, 1.15) | 28 (1/97) |
| Kingston, TN[c] | 1.09 (0.94, 1.25) | 1.09 (0.94, 1.26 | 30 (4/67) |
| Chicago, IL[h] | 1.04 (1.00, 1.08) | — | 37 (4/365) |
| Chicago, IL[g] | 1.03 (1.02, 1.04) | 1.02 (1.01, 1.04) | 38 (NR/128) |
| Utah Valley, UT[b] | 1.08 (1.05, 1.11) | 1.19 (0.96, 1.47) | 47 (11/297) |
| Birmingham, AL[d] | 1.05 (1.01, 1.10) | — | 48 (21, 80) |
| Los Angeles, CA[f] | 1.03 (1.00, 1.055) | 1.02 (0.99, 1.036) | 58( 15/177) |
| Increased Hospital Admissions (for Elderly > 65 yrs.) | | | |
| Respiratory Disease | | | |
| Toronto, CAN[I] | 1.23 (1.02, 1.43)[‡] | 1.12 (0.88, 1.36)[‡] | 30-39[*] |
| Tacoma, WA[J] | 1.10 (1.03, 1.17) | 1.11 (1.02, 1.20) | 37 (14, 67) |
| New Haven, CT[J] | 1.06 (1.00, 1.13) | 1.07 (1.01, 1.14) | 41 (19, 67) |
| Cleveland, OH[K] | 1.06 (1.00, 1.11) | — | 43 (19, 72) |
| Spokane, WA[L] | 1.08 (1.04, 1.14) | — | 46 (16, 83) |
| COPD | | | |
| Minneapolis, MN[N] | 1.25 (1.10, 1.44) | — | 36 (18, 58) |
| Birmingham, AL[M] | 1.13 (1.04, 1.22) | — | 45 (19, 77) |
| Spokane, WA[L] | 1.17 (1.08, 1.27) | — | 46 (16, 83) |
| Detroit, MI[O] | 1.10 (1.02, 1.17) | — | 48 (22, 82) |

**TABLE 13-3 (cont'd). EFFECT ESTIMATES PER 50 $\mu g/m^3$ INCREASE IN 24-h $PM_{10}$ CONCENTRATIONS FROM U.S. AND CANADIAN STUDIES**

| Study Location | RR (± CI) Only PM in Model | RR (± CI) Other Pollutants in Model | Reported $PM_{10}$ Levels Mean (Min/Max)[†] |
|---|---|---|---|
| Pneumonia | | | |
| Minneapolis, MN[N] | 1.08 (1.01, 1.15) | — | 36 (18,58) |
| Birmingham, AL[M] | 1.09 (1.03, 1.15) | — | 45 (19, 77) |
| Spokane, WA[L] | 1.06 (0.98, 1.13) | — | 46 (16, 83) |
| Detroit, MI[O] | — | 1.06 (1.02, 1.10) | 48 (22, 82) |
| Ischemic HD | | | |
| Detroit, MI[P] | 1.02 (1.01, 1.03) | 1.02 (1.00, 1.03) | 48 (22, 82) |
| Increased Respiratory Symptoms | | | |
| Lower Respiratory | | | |
| Six Cities[Q] | 2.03 (1.36, 3.04) | Similar RR | 30 (13,53) |
| Utah Valley, UT[R] | 1.28 (1.06, 1.56)[τ] | — | 46 (11/195) |
| | 1.01 (0.81, 1.27)[π] | | |
| Utah Valley, UT[S] | 1.27 (1.08, 1.49) | — | 76 (7/251) |
| Cough | | | |
| Denver, CO[X] | 1.09 (0.57, 2.10) | — | 22 (0.5/73) |
| Six Cities[Q] | 1.51 (1.12, 2.05) | Similar RR | 30 (13, 53) |
| Utah Valley, UT[S] | 1.29 (1.12, 1.48) | — | 76 (7/251) |
| Decrease in Lung Function | | | |
| Utah Valley, UT[R] | 55 (24, 86)[**] | — | 46 (11/195) |
| Utah Valley, UT[S] | 30 (10, 50)[**] | — | 76 (7/251) |
| Utah Valley, UT[W] | 29 (7,51)[***] | — | 55 (1,181) |

References:

[a]Schwartz et al. (1996a).
[b]Pope et al. (1992, 1994)/$O_3$.
[c]Dockery et al. (1992)/$O_3$.
[d]Schwartz (1993).
[g]Ito and Thurston (1996)/$O_3$.
[f]Kinney et al. (1995)/$O_3$, CO.
[h]Styer et al. (1995).
[I]Thurston et al. (1994)/$O_3$.
[J]Schwartz (1995)/$SO_2$.
[K]Schwartz et al. (1996b).
[L]Schwartz (1996).
[M]Schwartz (1994e).
[N]Schwartz (1994f).
[O]Schwartz (1994d).
[Q]Schwartz et al. (1994).
[P]Schwartz and Morris (1995)/$O_3$, CO, $SO_2$.
[R]Pope et al. (1991).
[S]Pope and Dockery (1992).
[T]Schwartz (1994g)
[W]Pope and Kanner (1993).
[X]Ostro et al. (1991)
[†]Min/Max 24-h $PM_{10}$ in parentheses unless noted otherwise as standard deviation (± S.D), 10 and 90 percentile (10, 90). NR = not reported.
[τ]Children.
[π]Asthmatic children and adults.
[*]Means of several cities.
[**]PEFR decrease in ml/sec.
[***]$FEV_1$ decrease.
[‡]RR refers to total population, not just>65 years.

## TABLE 13-4. EFFECT ESTIMATES PER VARIABLE INCREMENTS IN 24-h CONCENTRATIONS OF FINE PARTICLE INDICATORS ($PM_{2.5}$, $SO_4^=$, $H^+$) FROM U.S. AND CANADIAN STUDIES

| Acute Mortality | Indicator | RR (± CI) per 25 $\mu g/m^3$ PM Increase | Reported PM Levels Mean (Min/Max)[†] |
|---|---|---|---|
| Six City[A] | | | |
| Portage, WI | $PM_{2.5}$ | 1.030 (0.993, 1.071) | 11.2 (±7.8) |
| Topeka, KS | $PM_{2.5}$ | 1.020 (0.951, 1.092) | 12.2 (±7.4) |
| Boston, MA | $PM_{2.5}$ | 1.056 (1.038, 1.0711) | 15.7 (±9.2) |
| St. Louis, MO | $PM_{2.5}$ | 1.028 (1.010, 1.043) | 18.7 (±10.5) |
| Kingston/Knoxville, TN | $PM_{2.5}$ | 1.035 (1.005, 1.066) | 20.8 (±9.6) |
| Steubenville, OH | $PM_{2.5}$ | 1.025 (0.998, 1.053) | 29.6 (±21.9) |
| Increased Hospitalization | | | |
| Ontario, CAN[B] | $SO_4^=$ | 1.03 (1.02, 1.04) | R = 3.1-8.2 |
| Ontario, CAN[C] | $SO_4^=$ | 1.03 (1.02, 1.04) | R = 2.0-7.7 |
| | $O_3$ | 1.03 (1.02, 1.05) | |
| NYC/Buffalo, NY[D] | $SO_4^=$ | 1.05 (1.01, 1.10) | NR |
| Toronto[D] | $H^+$ (Nmol/$m^3$) | 1.16 (1.03, 1.30)[*] | 28.8 (NR/391) |
| | $SO_4^=$ | 1.12 (1.00, 1.24) | 7.6 (NR, 48.7) |
| | $PM_{2.5}$ | 1.15 (1.02, 1.78) | 18.6 (NR, 66.0) |
| Increased Respiratory Symptoms | | | |
| Southern California[F] | $SO_4^=$ | 1.48 (1.14, 1.91) | R = 2-37 |
| Six Cities[G] | $PM_{2.5}$ | 1.19 (1.01, 1.42)[**] | 18.0 (7.2, 37)[***] |
| (Cough) | $PM_{2.5}$ Sulfur | 1.23 (0.95, 1.59)[**] | 2.5 (3.1, 61)[***] |
| | $H^+$ | 1.06 (0.87, 1.29)[**] | 18.1 (0.8, 5.9)[***] |
| Six Cities[G] | $PM_{2.5}$ | 1.44 (1.15-1.82)[**] | 18.0 (7.2, 37)[***] |
| (Lower Resp. Symp.) | $PM_{2.5}$ Sulfur | 1.82 (1.28-2.59)[**] | 2.5 (0.8, 5.9)[***] |
| | $H^+$ | 1.05 (0.25-1.30)[**] | 18.1 (3.1, 61)[***] |
| Decreased Lung Function | | | |
| Uniontown, PA[E] | $PM_{2.5}$ | PEFR 23.1 (-0.3, 36.9) (per 25 $\mu g/m^3$) | 25/88 (NR/88) |

References:

[A]Schwartz et al. (1996a)
[B]Burnett et al. (1994)
[C]Burnett et al. (1995) $O_3$
[D]Thurston et al. (1992, 1994)
[E]Neas et al. (1995)
[F]Ostro et al. (1993)
[G]Schwartz et al. (1994)

[†]Min/Max 24-h PM indicator level shown in parentheses unless otherwise noted as (± S.D.), 10 and 90 percentile (10,90) or R = range of values from min-max, no mean value reported.
[*]Change per 100 nmoles/$m^3$
[**]Change per 20 $\mu g/m^3$ for $PM_{2.5}$; per 5 $\mu g/m^3$ for $PM_{2.5}$ sulfur; per 25 nmoles/$m^3$ for $H^+$.
[***]50th percentile value (10,90 percentile)

More recent reanalyses of the Harvard Six-City Study by Schwartz et al. (1996a) examined the effects on daily mortality of 24-h concentrations of fine particles ($PM_{2.5}$), inhalable particles ($PM_{15/10}$), or coarse fraction particles ($PM_{15/10}$ minus $PM_{2.5}$) as exposure indices. Note that inhalable particles are denoted here by $PM_{15/10}$ to reflect the change from the use of $PM_{15}$ cut point dichotomous samplers to $PM_{10}$ cut point samplers for later years of the study. The results were transformed to standard increments of 25 µg/m$^3$ $PM_{2.5}$, 50 µg/m$^3$ $PM_{15/10}$, and 25 µg/m$^3$ for the coarse fraction ($PM_{15/10-2.5}$) and are graphically depicted in Chapter 12, Figure 12-33. Of the three PM indices, $PM_{2.5}$ had the highest RR for daily mortality across the six cities. The only exception was for Steubenville, where a statistically significant coarse particle effect was found (although the fine particle effect size was as large as in most other cities and the fine and coarse particle concentrations were highly correlated in Steubenville). The acid aerosol relationships were weaker than were fine particle relationships, possibly because the acid aerosol time series were much shorter than the PM time series, as noted above.

In spite of differences in climate and demographics, the results showed that there were similar increases in daily mortality associated with fine particles in all six cities, with RR ranging from 1.020 to 1.056 per 25 $\mu$g/m$^3$ $PM_{2.5}$. The results were statistically highly significant in Harriman-Kingston, St. Louis, Watertown, nearly so in Portage and Steubenville, but less so in Topeka where the fine particle concentrations were low. The excess risk of death by ischemic heart disease associated with $PM_{2.5}$ was about 40% higher than for all-cause nonexternal mortality. For death due to pneumonia or due to COPD the excess risk was more than twice as high as for other causes. Only Steubenville, which had an RR = 1.061 per 25 $\mu$g/m$^3$ coarse-mode particles, showed results suggestive of possible excess risk from coarse particles. Overall, these analyses suggest that, in general, the association between excess mortality and thoracic particles appears to be stronger for the fine than the coarse fraction.

When data for all six cities were combined, the estimate of the effects of $PM_{15/10}$ and $PM_{2.5}$ were even more significant, with $PM_{2.5}$ having a higher associated risk than $PM_{15/10}$. The combined estimate for coarse mode particles ($PM_{15/10}$-$PM_{2.5}$), on the other hand, was only marginally significant. The combined effects estimates derived for the sulfate component was a statistically significant predictor of excess mortality (although less so than either $PM_{15/10}$ or $PM_{2.5}$), but $H^+$ was not statistically significant, even with 1,183 days of data in four cities. These results do not necessarily implicate sulfates as the key fine particle component associated with

mortality effects; rather, sulfates may represent a surrogate index for fine particles in general. Other studies in areas with low sulfate levels suggest that increased risk is also associated with non-sulfate fine particle components.

Relationships between chronic (annual average) PM exposures (Dockery et al., 1993) indexed by different particle size indicators ($PM_{15}$, $PM_{2.5}$, $PM_{15}$ to $PM_{2.5}$) and mortality effects as observed in the Harvard Six City Study were depicted graphically in Figure 12-8 of Chapter 12, emphasizing that there tends to be an increasing correlation of long-term mortality with PM indicators as they become more reflective of fine particle levels. These results are summarized in Table 13-5, along with findings from other key studies of U.S. and Canadian cities demonstrating associations between increased risk of mortality/morbidity and chronic (annual average) exposures to $PM_{10}$ or fine particle indicators in contemporary North American urban air sheds.

The effect estimate results for the studies in Table 13-3 are characterized in terms of relative risks (RR) corresponding to a specific PM increment (50 $\mu g/m^3$ $PM_{10}$) that generally encompass the range of the data within each study. As seen in Table 13-3, the mean 24-h $PM_{10}$ concentrations that were present during the studies generally ranged from 18 to 76 $\mu g/m^3$, with many of the highest daily values exceeding 100 $\mu g/m^3$. An indication of the potential for the occurrences of changes/increases of 24-h $PM_{10}$ levels of the magnitude of 50 $\mu g/m^3$ can be drawn from a data set of three years of daily levels of $PM_{10}$ in Philadelphia. During this study, the mean day-to-day differences seen in $PM_{10}$ concentration was 8.6 $\mu g/m^3$ with a maximum day-to-day variation of 50.4 $\mu g/m^3$. Maximum daily values by season were: summer - 82 $\mu g/m^3$; winter - 77.5 $\mu g/m^3$; spring - 54.7 $\mu g/m^3$; and fall - 54.4 $\mu g/m^3$. The difference between the median and maximum value for summer was 54.4 $\mu g/m^3$ and for winter, 58.3 $\mu g/m^3$.

***Acid Aerosol Mortality Effects***

Several epidemiologic studies have measured the mass of acidic aerosols or sulfates. This acid aerosol mass would primarily be found in the fine PM fraction, that is in ambient fractions < $PM_{2.5}$. Studies of past episodes suggest that there can be both acute and chronic

## TABLE 13-5. EFFECT ESTIMATES PER INCREMENTS[a] IN ANNUAL MEAN LEVELS OF FINE PARTICLE INDICATORS FROM U.S. AND CANADIAN STUDIES

| Type of Health Effect & Location | Indicator | Change in Health Indicator per Increment in PM[a] | Range of City PM Levels Means ($\mu g/m^3$) |
|---|---|---|---|
| Increased total chronic mortality in adults | | Relative Risk (95% CI) | |
| Six City[b] | $PM_{15/10}$ | 1.42 (1.16-2.01) | 18-47 |
| | $PM_{2.5}$ | 1.31 (1.11-1.68) | 11-30 |
| | $SO_4^=$ | 1.46 (1.16-2.16) | 5-13 |
| ACS Study[c] (151 U.S. SMSA) | $PM_{2.5}$ | 1.17 (1.09-1.26) | 9-34 |
| | $SO_4^=$ | 1.10 (1.06-1.16) | 4-24 |
| Increased bronchitis in children | | Odds Ratio (95% CI) | |
| Six City[d] | $PM_{15/10}$ | 3.26 (1.13, 10.28) | 20-59 |
| Six City[e] | TSP | 2.80 (1.17, 7.03) | 39-114 |
| 24 City[f] | $H^+$ | 2.65 (1.22, 5.74) | 6.2-41.0 |
| 24 City[f] | $SO_4^=$ | 3.02 (1.28, 7.03) | 18.1-67.3 |
| 24 City[f] | $PM_{2.1}$ | 1.97 (0.85, 4.51) | 9.1-17.3 |
| 24 City[f] | $PM_{10}$ | 3.29 (0.81, 13.62) | 22.0-28.6 |
| Southern California[g] | $SO_4^=$ | 1.39 (0.99, 1.92) | — |
| Decreased lung function in children | | | |
| Six City[d,h] | $PM_{15/10}$ | NS Changes | 20-59 |
| Six City[e] | TSP | NS Changes | 39-114 |
| 24 City[i,j] | $H^+$ (52 nmoles/$m^3$) | −3.45% (-4.87, -2.01) FVC | — |
| 24 City[i] | $PM_{2.1}$ (15 $\mu g/m^3$) | −3.21% (-4.98, -1.41) FVC | — |
| 24 City[i] | $SO_4^=$ (7 $\mu g/m^3$) | −3.06% (-4.50, -1.60) FVC | — |
| 24 City[i] | $PM_{10}$ (17 $\mu g/m^3$) | −2.42% (-4.30, -.0.51) FVC | — |

[a]Estimates calculated annual-average PM increments assume: a 100 $\mu g/m^3$ increase for TSP; a 50 $\mu g/m^3$ increase for $PM_{10}$ and $PM_{15}$; a 25 $\mu g/m^3$ increase for $PM_{2.5}$; and a 15 $\mu g/m^3$ increase for $SO_4^=$, except where noted otherwise; a 100 nmole/$m^3$ increase for $H^+$.
[b]Dockery et al. (1993)
[c]Pope et al. (1995)
[d]Dockery et al. (1989)
[e]Ware et al. (1986)
[f]Dockery et al. (1996)
[g]Abbey et al. (1995a,b,c)
[h]NS Changes = No significant changes.
[i]Raizenne et al. (1996)
[j]Pollutant data same as for Dockery et al. (1996)

health effects of strongly acidic PM. Studies of historical pollution episodes, notably the London Fog episodes of the 1950's and early 1960's, indicate that acute exposures to extreme elevations of 24-h acid aerosol concentrations may be associated with excess daily human mortality when present at times of elevated concentrations of BS and $SO_2$. In addition, significant associations were found between acid aerosols ($\leq$ 30 $\mu g/m^3$ as $H_2SO_4$, 24-h or $\leq \sim$600 nmoles/$m^3$ $H^+$, 24-h) and mortality in London during non-episode pollution periods of the 1960s and 1970s, though these associations could not be separated from those for BS or $SO_2$. Studies evaluating present-day U.S. levels of acidic aerosols have not found associations between acid aerosols and acute and chronic mortality, but the series of $H^+$ data used may not have been long enough to detect $H^+$ associations.

Based on laboratory animal toxicology studies, it is known that sulfuric acid aerosols exert their action throughout the respiratory tract, with the site of deposition dependent upon particle size and the response dependent on mass and number concentration at specific deposition sites. At very high concentrations that are not environmentally realistic, mortality can occur in toxicological studies following acute exposure, due primarily to laryngospasm or bronchoconstriction; larger acidic particles may be somewhat more potent in this regard than smaller ones. As seen in these studies, extensive pulmonary damage, including edema, hemorrhage, epithelial desquamation, and atelectasis can also cause death, but even in the most sensitive animal species, lethal concentrations are at least a thousand-fold greater than current ambient levels.

The available laboratory animal findings regarding acid aerosols provide no evidence that ambient acidic PM components contribute to mortality and essentially no quantitative guidance as to the ambient PM levels at which mortality would be expected to occur in either healthy or diseased humans. The laboratory animal effects were observed at acid levels that exceed worst-case ambient concentrations by more than ten-fold. Also, since the inhalable particle size range for common laboratory animals is generally < 2 to 4 $\mu$m, only comparisons between inhalable and ultrafine particles were possible. There were no obvious differences between responses of laboratory animals exposed to ultrafine acid aerosol as compared to larger inhalable acidic aerosols (see Section 13.6.7).

***Shortening of Life Associated with Ambient PM Exposure***

The public health burden of ambient PM-mediated mortality depends on both the number of deaths and the shortening of life that PM exposure causes or promotes. Knowledge of the true excess mortality and prematurity of death attributable to PM would be valuable to environmental risk managers and scientists in predicting and monitoring the public health benefit of reducing ambient PM exposure.

Epidemiologic findings suggest that short-term ambient PM exposure can trigger terminal events. Also, long-term PM exposure could conceivably promote life-shortening chronic illness. The relative risk ratios derived from long-term U.S. cohort studies of PM exposure and mortality are considerably larger than those from daily mortality studies. This suggests that a portion of deaths associated with long-term PM exposure may be independent of the daily deaths associated with short-term exposure and/or that some factor not accounted for may be contributing to these effects. In both long-term and short-term studies, the PM associations with mortality are strongest in the elderly for respiratory and cardiovascular causes of death.

Available experimental evidence provides only minimal biological understanding of PM's true role in influencing mortality. At the same time, several general pathways by which long-term and short-term PM exposure might plausibly increase mortality have been postulated. For example, long-term PM exposure might promote life-shortening chronic respiratory illness, the terminal event of which could be infection or other insult unrelated to recent PM exposure. Conversely, episodic short-term PM exposure might trigger death in highly susceptible persons with preexisting severe illnesses unrelated to long-term PM exposure. Or, in some individuals, ambient PM exposures might both promote chronic illness and trigger death. Emerging experimental evidence indicates that all of these should be considered as possibilities.

Confident quantitative determination of years of life lost to ambient PM exposure is not yet possible; life shortening may range from days to years. Two recent epidemiologic analyses (Spix et al., 1993; Cifuentes and Lave, 1996) suggest that some portion of PM-induced daily mortality occurs in people who are already so ill that they would soon die even without PM exposure. In addition to non-episodic increase in PM-related mortality, Cifuentes and Lave estimate that 37 to 87% of the adult deaths occurring during identifiable short-term PM episodes may be premature by only a few days. The public health implications of this estimate are not yet clear because the proportion of all PM-associated daily deaths occurring during episodes, and the

strengths of PM-daily mortality relationships during episodes relative to other periods, have not been determined.

The upper limit of PM-associated life shortening is not known and will also be difficult to determine. Available evidence regarding the effect of smoking on mortality may be of some contextual use in estimating this limit. Davis and Novotny (1989) investigated smoking-attributable mortality and years of life lost to smoking in chronic obstructive pulmonary disease (COPD). They reported that, in 1984, 51,013 (79.4%) of a calculated total of 64,211 COPD deaths in the U.S. were attributable to smoking and that 82% of these deaths occurred in persons aged at least 65 years. These smoking-attributable deaths represented a total of 501,290 years of life lost in relation to average life expectancy. These figures yield an average of 9.8 years of life lost per smoking-attributable COPD death. It is highly unlikely that PM-attributable life shortening would approach or exceed this average at current ambient U.S. PM levels. Nevertheless, life shortening could conceivably be on the order of years, especially if smoking and PM exposure exert synergistic long-term effects in COPD.

In summary, most available epidemiologic evidence suggests that increased mortality results from both short-term and long-term ambient PM exposure. Limitations of available evidence prevent quantification of years of life lost to such mortality in the population. Life shortening, lag time, and latent period of PM-mediated mortality are almost certainly distributed over long time periods, although these temporal distributions have not been characterized. Increased biological understanding of PM's role in relevant mechanisms is essential to guide further epidemiologic study of these complex issues.

### 13.4.1.2 Ambient PM Morbidity Effects

Consistent with the above-noted observations of PM-induced mortality effects, numerous epidemiologic studies in the U.S. and elsewhere have demonstrated significant associations between ambient PM exposures indexed by a variety of indicators (BS, TSP, $PM_{10}$, $PM_{2.5}$, sulfates, etc.) and various acute and chronic morbidity outcomes. Such outcomes include, for example, hospital admissions, increased respiratory symptoms, and decreased lung function. Tables 13-3 to 13-5 provide effect estimates for various PM indicators drawn from recent U.S. and Canadian studies thought to provide reasonably credible quantitative estimates that are likely

representative of the range of increased mortality and morbidity risks associated with ambient exposures to PM in contemporary U.S. urban air sheds.

***Hospitalization and Outpatient Visits***

Potentially, the most severe morbidity measure evaluated with regard to PM exposure is hospitalization with a cardiopulmonary diagnosis. This outcome is relevant to the PM-mortality relationships discussed above. Some morbidity outcomes require hospitalization immediately, while others may require several days of progression to end in an admission. Exposure-response lag periods are not yet well examined for hospital admissions related to PM exposures.

Both COPD and pneumonia hospitalization studies show moderate but statistically significant relative risks in the range of 1.06 to 1.25 resulting from an increase of 50 $\mu g/m^3$ in $PM_{10}$ or its equivalent. There is a suggestion of a relationship between ambient $PM_{10}$ and heart disease admissions, but the estimated effects are smaller than those for other endpoints (see Figure 12-1 in Chapter 12). While a substantial number of hospitalizations for respiratory illnesses occur in those $\geq$65 years of age, there are also numerous hospitalizations for those under 65 years of age. Several of the hospitalization studies restricted their analysis by age of the individuals, but did not explicitly examine younger age groups. One exception was Pope (1991) who reported an increase in hospitalization for Utah Valley children (aged 0 to 5) for monthly numbers of admissions in relation to $PM_{10}$ monthly averages, as opposed to daily admissions in relation to daily PM levels used in other studies.

Studies examining associations between other indicators of fine particles, e.g., British smoke (BS), or indicators of total particle concentrations (TSP) and hospital admissions also report finding significant relationships. One study in Spain, for example, found a statistically significant association between changes in hospital admissions and BS during the winter season. Also, in Finland, TSP was found to be significantly correlated with hospitalization admissions for asthma. For those age 65 or older in Philadelphia, hospitalization for pneumonia showed a RR at about 1.22 (1.10 to 1.36) corresponding to an increase of 100 $\mu g/m^3$ of TSP.

Increased hospital admissions for respiratory causes documented during the 1952 London Fog episode suggested an association with sulfuric acid aerosols as well as with BS and $SO_2$ measurements. More recent studies have shown a consistent relationship between summertime levels of both sulfates and $O_3$ with hospital admissions. Two Canadian studies estimated a 3 to

4% increase in annual respiratory hospital admissions for about a 13 to 14 $\mu g/m^3$ increase in concentration of the sulfate fraction. A corresponding 2 to 3% increase in cardiac admissions was reported in one of these studies. While sulfates have been predictive of health effects in some studies, it is not clear whether the sulfate-related effects can be attributed to their acidity or other characteristics, or if they are more broadly related to fine particles in general. Another study found associations between ambient acidic aerosols and summertime respiratory hospital admissions both in New York State and Toronto, Canada, even after controlling for potentially confounding temperature effects. In the Toronto analysis, the increase in respiratory hospital admissions associated with $H^+$ was roughly six times that for non-acidic $PM_{10}$ (per unit mass). In these analyses $H^+$ effects were estimated to be the largest during acid aerosol episodes (days) ($H^+ \geq 10$ $\mu g/m^3$ as $H_2SO_4$, or $\approx$200 nmoles/$m^3$ $H^+$), which occur roughly 2 to 3 times per year in eastern North America. Sulfate concentrations that were previously found to be correlated with respiratory admissions are associated with acidic aerosols in Eastern North America. In these recent analyses, the $H^+$ associations with respiratory hospital admissions were found to be stronger than for sulfates or any other PM component monitored. This Toronto study showed no associations for $PM_{10}$-$PM_{2.5}$ or for TSP-$PM_{10}$ measures of coarse particles. Other studies, which did not directly measure coarse particles, have evaluated situations where PM was dominated by coarse particles. Gordian et al. (1996) reported increased outpatient visits for asthma and upper respiratory illness, but not for bronchitis in Anchorage, Alaska where $PM_{10}$ contains primarily coarse particle-crustal material and volcanic ash. Hefflin et al. (1994) determined that the maximum observed/expected ratio was 1.2 for respiratory disorders resulting from dust storms on October 16 and 21, 1991 which produced the highest $PM_{10}$ levels of 1991 (i.e., 1,689 and 1,035 $\mu g/m^3$, respectively) in southeast Washington state. $PM_{10}$ was considered to be mostly from natural sources as compared to industry or combustion sources. In both of these studies, numerous marked exceedances of the $PM_{10}$ standards occurred.

***Community-Based Respiratory Illness and Pulmonary Function Studies***

Acute respiratory illness studies may include several different endpoints, but typically present results for: (1) upper respiratory illness, (2) lower respiratory illness, or (3) cough (as summarized earlier in Chapter 12, Figure 12-5). The studies of upper respiratory illness do not show a consistent relationship with PM, although some of this inconsistency could be explained

by the differences in populations studied. The studies of lower respiratory disease, however, yielded odds ratios (OR) which ranged from 1.10 to 1.28, and studies of cough gave odds ratios ranging from 0.98 to 1.29 (note that the odds ratios were estimated for a 50 $\mu g/m^3$ increase in $PM_{10}$ or its equivalent). An exception in each of the latter two categories was the Six City study which produced ORs of 2.0 and 1.51 for lower respiratory disease and cough, respectively. These three respiratory illness endpoints had similar general patterns of results. The odds ratios were generally positive, the 95% confidence intervals for about half of the studies were statistically significant (i.e., the lower bound exceeded 1.0) and, for each endpoint, one study had a high odds ratio. Limited data were available relating PM exposure to asthma or respiratory symptoms in adults.

As part of the Six Cities studies, three analyses done for different time periods suggest a chronic effect of PM exposure on respiratory disease. Chronic cough, chest illness, and bronchitis showed positive associations with PM for the earlier surveys. A recent study is strongly suggestive of an effect on bronchitis from acidic particles or from other PM.

Pulmonary function studies (summarized in Chapter 12, Figure 12-6) are suggestive of short term effects resulting from particulate exposure. Peak expiratory flow rates show decreases in the range of 2 to 5 l/min resulting from an increase of 50 $\mu g/m^3$ in $PM_{10}$ or its equivalent, with somewhat larger effects in symptomatic groups such as asthmatics. Studies using $FEV_1$ or FVC as endpoints show less consistent effects. For comparison, a passive smoking study of over 16,000 children found that maternal smoking decreased a child's $FEV_1$ by 10 to 30 ml. An estimate of the effect of PM on pulmonary function in adults found a 29 (±10) ml decrease in $FEV_1$ per 50 $\mu g/m^3$ increase in $PM_{10}$, which is similar in magnitude to the changes found in children, although a smaller percent change.

The chronic pulmonary function studies are less numerous than the acute studies and the results are inconclusive. The Six-City studies, which had good monitoring data, showed no associations of chronic pulmonary function effects with long-term particulate pollution measurements. Other studies found small, but statistically significant, decreases in FVC in healthy non-smokers or other pulmonary function effects that may be attributed to either acidic particles or PM in general. The absence of a strong association between chronic pulmonary function changes and PM calls into question the viability of one of the hypothetical mechanisms

for chronic PM-mortality relationships, namely the acceleration of the age-related decline in pulmonary function.

In addition to respiratory symptoms, bronchitis prevalence rates reported in the Six-City study were found to be more closely associated with annual average $H^+$ concentrations than with PM in general. As mentioned earlier, in a study of children in 24 U.S. and Canadian communities, bronchitis symptoms were shown to be significantly associated with strongly acidic PM. Thus, chronic exposures to strongly acidic PM may have effects on measures of respiratory health in children. The acid levels were highly correlated to other fine particle indicators such as $PM_{2.1}$, as noted previously.

Overall, the morbidity studies qualitatively indicate that acute PM exposures are associated with hospital admission for respiratory disease, increased occurrence of respiratory disease symptoms, and pulmonary function decrements. As stated above, hospitalization studies and acute pulmonary function changes suggest quantitative relationships. Also, some limited evidence exists for association of ambient acidic aerosol exposures with increased acute or chronic respiratory symptoms.

***Comparison of $PM_{10}$ Versus $PM_{2.5}$ Exposure Effects on Morbidity***

Dosimetry models predict that total deposition of fine mode particles in the alveolar region of the lower respiratory tract (alveoli, terminal bronchioles) is somewhat greater than in the tracheobronchial region. It is therefore important to consider whether exposure indices for the fine fraction (e.g., $PM_{2.5}$) show larger and more significant effects than indices that also include coarse particles (e.g., $PM_{10}$), which may have a greater deposition efficiency in the larger and more proximal airways. Mechanistic effects caused by PM in these different lower respiratory tract regions may be different, potentially leading to different health outcomes. While numerous studies of PM related respiratory morbidity have been conducted using $PM_{10}$ as an indicator, only limited numbers of studies have examined the effects of fine particle indicators such as $PM_{2.5}$. Obviously, the only meaningful direct comparison of the effect of $PM_{10}$ to $PM_{2.5}$ is provided when a study includes both exposure measures and evaluates effects in relation to the coarse fraction $PM_{(10-2.5)}$ as well. $PM_{10}$ was a better predictor of respiratory disease in the Six-City study, whereas $PM_{2.5}$ was a better predictor of pulmonary function effects in Tucson, where coarse particles likely represent a larger fraction of $PM_{10}$ than in eastern U.S. cities. Other

studies using $PM_{2.5}$ to evaluate acute morbidity have not provided information that permits assessment of these two exposure indices with regard to health outcomes.

Two more recent chronic exposure studies permit comparison of results for $PM_{10}$, $PM_{2.1}$, and particulate acidity. Children living in communities with the highest levels of particle strong acidity were more likely (OR = 1.66, 95% CI = 1.11, 2.48) to report at least one episode of bronchitis in the past year compared to children living in communities with the lowest levels of acidity. The odds ratios for bronchitis were similar at 1.50 (increment of 15 $\mu g/m^3$; 95% CI = 0.91, 2.47) for $PM_{2.1}$ and 1.50 (increment of 17 $\mu g/m^3$; 95% CI = 0.93 to 2.43) for $PM_{10}$, respectively. No other respiratory symptoms, including asthma symptoms, were significantly associated with any of the pollutants. The strong correlations between several of the pollutants in this study, especially particle strong acidity with sulfate (r = 0.90) and $PM_{2.1}$ (r = 0.82), make it difficult to distinguish the agent of most interest.

In children, a 52 nmole/$m^3$ difference in annual mean particle strong acidity was associated with a 3.5% deficit in FVC (adjusted) and a 3.1% deficit in $FEV_1$ (adjusted) with a slightly larger deficit in lifelong residents of their communities. Slightly smaller deficits were seen using total sulfate, $PM_{2.1}$, and $PM_{10}$ as pollutant exposure measures, and these deficits were also statistically significant.

These few studies on $PM_{2.5}$ show morbidity effects that are difficult to separate both from $PM_{10}$ measures and acid aerosol measures discussed above. The $PM_{2.5}$ studies do show effects related to exposure to the fine fraction. However, high correlations among $PM_{2.5}$, $PM_{10}$, and acid aerosols make it very difficult to distinguish among these exposure indicators.

Other information suggests that coarse PM effects may warrant continued attention. There are epidemiological findings of physician visits for asthma associated with coarse crustal PM (e.g., Gordian et al., 1996). Also, therapeutic aerosols used in the treatment of asthma are generally in a size range from 2.5 to 5 $\mu$m, although greatest penetration into the lung is with the particles at the lower end of this range (i.e., 2.5 to 3.0 $\mu$m) (Kim et al., 1985). Thus, particles in the coarse fraction of $PM_{10}$ appear to be associated with the exacerbation of asthma via ambient exposure, and analogous sized aerosols are used in the treatment of asthma via metered-dose inhalers.

## 13.4.2 Assessment of Validity and Coherence of Epidemiologic Findings

### 13.4.2.1 Human Exposure Assessment: Uncertainties and Implications

To varying extents, all available epidemiologic studies are subject to uncertainty in assessment of individual subjects' exposures to ambient PM and other air pollutants. Studies of PM are especially prone to such uncertainty because PM is physically and chemically far more complex than any other NAAQS pollutant. Such uncertainty tends to be greatest in hospitalization and mortality studies, because measurements from limited numbers of ambient monitoring stations have generally been applied to large populations in broad geographic areas, without adjustment for factors affecting individuals' indoor and personal exposures. Individual exposure estimates have seldom been made in available epidemiologic studies, and remain subject to much uncertainty even when available.

Even at fixed outdoor stations, accurate, thorough measurement of ambient PM size distributions and chemical constituents is technologically challenging and expensive. Ambient measurements are not yet available in sufficient accuracy or detail to enable thorough comparison of the potencies of specific constituents of the PM complex. For example, few direct measurements of $PM_{2.5}$ and inhalable coarse fraction PM, and no size-specific measurements of PM < 1.0 $\mu$m, are yet available for epidemiologic assessment. Similarly, beyond sulfates, nitrates, and to some extent $H^+$ and organic compounds, specific chemical components of PM have yet to be extensively epidemiologically assessed. Thus, for example, very little biomedical information has yet been analyzed against levels of the non-sulfate fraction of $PM_{2.5}$. Despite these limitations, several salient points appear to be emerging from assessment of currently available information.

For example, although generally useful for qualitative epidemiologic demonstration of PM effects, TSP measurements can include large coarse-mode particles that exceed the inhalable range. Thus, TSP can reasonably be expected to provide "noisy" estimates of exposure-effect relationships if such relationships are due to inhalable particle fractions of the measured TSP mass. $PM_{10}$ is a better index of the inhalable particles than is TSP, and $PM_{10}$ may be a better index of ambient fine particle exposure than TSP because the smaller particulate fraction contained in $PM_{10}$ is more uniformly distributed in an urban area or region than are larger coarse particles also indexed by TSP.

As discussed in Section 13.2.6, $PM_{2.5}$ particles are generally likely to be more uniformly distributed than coarse particles within an urban airshed. For example, while $PM_{10}$ levels vary from site to site, $PM_{2.5}$ levels have been shown to be particularly well correlated across at least one eastern metropolitan region, i.e., Philadelphia (Burton et al., 1996; Wilson and Suh, 1996). Also as noted earlier, fine particles are at least as likely to infiltrate indoors as are coarse particles, but the fine particles are removed less rapidly from indoor air than coarse particles. Thus, outdoor ambient fine particle concentrations may be better predictors of total human exposure to ambient fine particles than ambient coarse particle concentrations are of total exposure to ambient coarse particles.

Overall, then, it appears that size-specific fixed-station ambient PM measurements generally approximate total ambient fine PM exposure more closely than coarse PM exposure. Within the fine fraction, fixed-station measurements of ambient $SO_4^=$ likely approximate total exposure to sulfates better than similar measurements of $H^+$ would index total $H^+$ exposure, because a higher proportion of $SO_4^=$ persists indoors ($H^+$ is neutralized by indoor ammonia). Furthermore, because misclassification of exposure tends to bias toward the null hypothesis, the larger error in ambient coarse PM and $H^+$ estimates could produce more underestimation of effects of coarse than of fine PM, and of $H^+$ than of $SO_4^=$. On balance, available health effects estimates, whatever their magnitude and direction, are more subject to uncertainty for coarse than for fine PM, and for $H^+$ than $SO_4^=$.

Difficulties in distinguishing between possible differences in health effects from particles of various sizes and chemistries that fluctuate together also represent a limitation in interpreting existing long-term PM exposure studies. Cross-sectional and prospective cohort studies have reported significant mortality associations for fine particles, indexed by $PM_{2.5}$ (Dockery et al.,

1993) or sulfates (Ozkaynak and Thurston, 1987). However, significant PM/mortality associations have also been reported in areas where summertime sulfates are not the major component of PM (e.g., winter analysis of Santa Clara, CA; Los Angeles, CA).

### 13.4.2.2 Model Selection/Specification Issues

Model selection/specification issues assume many forms, including distributional assumptions, assumptions about temporal structure or correlation, assumptions about random and systematic components of variability, assumptions about the shape of the relationship between response and covariate, and assumptions about additivity and interactions of covariates. Most studies evaluate some of these model specification issues, but rarely provide enough information for the reader to independently assess the conclusions. Some of the model specification issues have been shown to have the potential for substantially modifying the conclusions reached by the analyses. The most sensitive model specification issues appear to be: adjustments for seasonality and for long-term time trends; adjustments for co-pollutants; and adjustments for weather variables. An in depth discussion of model specification for acute mortality studies, is presented in Section 12.6.2, where $PM_{10}$ studies of mortality are reviewed and analyzed (Pope et al., 1992; Ostro et al., 1996; Dockery et al., 1992; Thurston and Kinney, 1995; Kinney et al., 1995; Ito et al., 1995; Styer et al., 1995). Also, importantly, alternative TSP mortality analyses for the same city, Philadelphia (Moolgavkar et al., 1995, Li and Roth, 1995; Wyzga and Lipfert, 1995; Cifuentes and Lave, 1996; Samet et al., 1995; Schwartz and Dockery, 1992b) are reviewed and analyzed.

Differences in model specification may produce important differences in estimates of PM effects. The general concordance of PM effects estimates, particularly in the analyses of short-term mortality studies, is a consequence of certain appropriate choices in modelling strategy that most investigators have adopted using several different types of standardized models (GLM, LOESS, etc.) and a variety of specific specifications. For example, in short-term studies of mortality or hospital admissions, it is important that large differences occurring over time be extracted before assessing short-term changes in health effects attributable to concurrent short-term changes in air pollution. However, several methods appear to be adequate for carrying out such adjustments, including nonparametric detrending, use of indicator variables for season and year, and (in older studies) filtering. The largely consistent specific results, indicative of

significant positive associations of ambient PM exposures and human mortality/morbidity effects, are not model-specific, nor are they artifactually derived due to misspecification of any specific model. The robustness of the results of different modelling strategies and approaches increases confidence in their validity.

### 13.4.2.3 Evaluation of Potential Influences Due to Weather

A variety of methods also appear to be capable of adequately adjusting time series data for the effects of weather. Most PM epidemiology studies use temperature and dewpoint as covariates, with several parametric models (possibly differing by season) and nonparametric smoothing models appearing to be adequate. Other weather variables, such as changes in barometric pressure, may also be predictive. Models that used synoptic weather categories as indicator variables, in which the categories were defined independently of information about the health effect, provide a plausible *a priori* basis for weather covariate adjustments as Pope and Kalkstein (1996) have shown for the Utah Valley study. At this time, relatively few studies have examined possible statistical interactions between weather and air pollution (Lipfert and Wyzga, 1995). While the role of weather-related variables is clearly important, this issue appears to have been adequately addressed in most of the recent studies reviewed in Chapter 12, and the relative insensitivity of PM coefficients to different methods of weather adjustment has been demonstrated in these studies including recently reported reanalyses of several data sets by HEI. While weather clearly affects human health, there does not seem to be much basis for believing that weather can explain a substantially greater part of the health effects attributed to PM than has already been accounted for by the empirical models used in the health studies assessed in Chapter 12.

### 13.4.2.4 Evaluation of Potential Influences of Co-pollutants

Other pollutants such as $SO_2$, $O_3$, and CO play a role in modifying the relationship between PM and mortality. When they are incorporated into models examining these relationships, the RR is usually smaller. Multi-pollutant models can cause differences in interpretation for a single-pollutant model such as when the correlation between PM and the other pollutants is sufficiently high that attributed health outcomes are shared among the pollutants. The most

poorly measured pollutant is usually the one that is driven toward no statistically significant estimate of effect.

Some of the studies cited in Chapter 12 include substantial assessments of the effect of potential confounding from co-pollutants. It was possible to carry out a statistical adjustment for co-pollutants in some studies, with the PM effect size estimated with and without the potential confounder in the model. The PM effect size estimates and their statistical uncertainty in many studies showed little sensitivity to the adjustment for co-pollutants. However, in some other analyses where was substantial confounding with co-pollutants such as $SO_2$ or $O_3$, estimates of RR for PM without inclusion of the confounders in the statistical concentration-effect model used in these studies were quantitatively similar to RR estimates from other studies where confounding was either avoided or was shown statistically to have little effect. This includes cases where PM effects were demonstrated in cities with very low levels of other major copollutants present, as well as in cities with moderate to high levels of one or another copollutant.

Some investigators have noted that similarity of PM regression coefficients in single and multi-pollutant models is sufficient to show that PM is not confounded by the other pollutants. When the RR estimates for PM are relatively unchanged and there is little increase in the width of the confidence interval, then one can say there is little evidence of confounding. For example, in the Utah Valley mortality study (Pope et al., 1992), the RR estimates for the summer season and the width of the confidence intervals for $PM_{10}$ were similar whether the model did not include ozone, included daily average ozone, or used maximum daily 1-h ozone as the co-pollutant measure. The summer PM coefficient, with or without ozone, is similar to the winter value, when ozone levels were so low as to have little probable effect on mortality, which illustrates both covariate adjustment and confounder avoidance strategies in the same study.

The model for the Los Angeles mortality studies (Kinney et al., 1995) evaluated the results of including co-pollutants, $O_3$ and CO. Including $O_3$ in the model along with $PM_{10}$, did not change the RR for PM, but increased its uncertainty slightly so that the RR for PM was now only marginally significant. Including CO in the model reduced the RR for PM which was also less significant. Thus, the PM-mortality association was not completely separable from other copollutants. A sensitivity analysis by Schwartz and Dockery (1992b) for mortality in Steubenville indicates that including $SO_2$ reduced the TSP effect. However, the decrease was

small with RR for TSP only decreasing from 1.04 without including $SO_2$ to 1.03 per 100 $\mu g/m^3$ when $SO_2$ was included.

Most studies have provided very little empirical basis for the reader to assess the adequacy of the fitted model, especially for analyses involving copollutants. The HEI report (Samet et al., 1995) presents three-dimensional surfaces showing the smoothed or fitted mortality response versus TSP and $SO_2$ for the 1973 to 1980 Philadelphia data set. These analyses indicate that both TSP and $SO_2$ were associated with significant increases in mortality but there were important differences in effect depending on season and on the range of TSP or $SO_2$ values. There was a relationship between $SO_2$ and excess mortality at TSP concentrations below 75 $\mu g/m^3$, but the relationship was not evident at above 50 ppb $SO_2$ or above 75 to 100 $\mu g/m^3$ TSP concentration. Thus, it is clearly not correct to conclude from the additive linear model results that one pollutant is always (or never) a better predictor of excess mortality in Philadelphia than is the other pollutant. The Samet et al. (1995) analyses suggest that concluding from an additive linear model that inclusion of copollutants generally lowers the effect attributable to PM may not always apply to a more accurate nonparametric model.

Recent reanalyses of the Philadelphia mortality-TSP data (Moolgavkar et al., 1995b; Wyzga and Lipfert, 1995; Samet et al., 1995, 1996a; Cifuentes and Lave, 1996) have elucidated some of the complex issues relating to analyses of urban air pollution mixtures. The first point is that the relationship between mortality and different air polluitants may be different from season to season. This may be due, in part, to substantial seasonal differences in the correlation structure among the multiple pollutants in the urban airshed (Samet et al., 1996a, discussed in Section 12.6). Furthermore, there may be additional interactions within each season involving TSP and temperature (Wyzga and Lipfert, 1995), although a study of TSP and synoptic weather categories in Utah Valley found little evidence for interaction of $PM_{10}$ and weather (Pope and Kalkstein, 1996).

Secondly, while some studies find that including $O_3$ in a model with TSP can modify the estimated TSP seasonal effect (Moolgavkar et al., 1995b), other studies find that $O_3$ has a significant additive effect on mortality that is largely unconfounded with the TSP or $SO_2$ effects (Cifuentes and Lave, 1996; Samet et al., 1996a). CO has little effect on mortality, as does $NO_2$ by itself, but including $NO_2$ in a model with either TSP and $SO_2$ tends to increase the effects of both (Samet et al., 1996a). While TSP, $SO_2$, $NO_2$, CO, and $O_3$ are modestly correlated in the

Philadelphia studies, these correlations are not so high as to preclude the possibility of identifying separate air pollutant effects in different seasons (discussed in Section 12.6).

Thirdly, the relationship between TSP, $SO_2$, and mortality may be intrinsically nonlinear (Samet et al., 1995; Cifuentes and Lave, 1996). The additive linear models used in most studies to assess effects of copollutants may therefore not be adequate to characterize the more complex nonlinear interrelationships among them.

Finally, the estimated TSP effects for Philadelphia are quantitatively similar to those in other studies. Estimates of effects using PM indicators in communities where $SO_2$ concentrations are low, such as Utah Valley, are also similar. While there is difficulty in separating TSP and $SO_2$ effects in Philadelphia, the results are not anomalous compared to those in other cities.

Confounding by co-pollutants sometimes cannot be avoided. In studies where sensitivity analyses demonstrate that including other pollutants in the model cause little change in either the RR estimate for PM or the width of the confidence interval for the PM effect, one may conclude that the model is not seriously confounded by co-pollutants. Some studies of PM-related mortality or morbidity have shown the specific relative risk estimates for PM only in the respective models to be little changed by inclusion of other co-pollutants in the model, suggesting little confounding in those cases. On the other hand, in those analyses where the RR estimate for PM was notably diminished by inclusion of other co-pollutants in the model (indicative of some confounding), the PM effect typically still remains statistically significant, although reduced. Since a number of mortality and morbidity studies have shown that the PM effect on health is not sensitive to other pollutants, we may conclude that findings regarding the PM effects are valid.

### 13.4.2.5 Coherence of Epidemiologic Findings

Factors involved in evaluating both the data and the associations between exposure variables and outcome variables derived from epidemiological studies, include the strength of the association; the consistency of the association, as evidenced by its repeated observation by different investigators, in different places, circumstances and time; and the consistency of the association with other known facts (Bates, 1992). To provide a more comprehensive synthesis of available information, coherence or the logical or systematic interrelationships between

different health indices, should be evaluated. Making the case for causality in regard to observed epidemiologic associations would be further strengthened by biological plausibility, consistency or replication of findings, and coherence. The difficulty with discussing any index of internal coherence is that it requires a series of judgments on the reliability of the individual findings and observations. Thus the outcome of a coherence discussion is qualitative not quantitative. Bates (1992) also noted that the strength of the association of different health indices with exposure are important, as are difficulties in assessing exposure, and suggests three areas to look for coherence: (1) within epidemiological data, (2) between epidemiological and animal toxicological data, and (3) among epidemiological, controlled human and animal data.

Coherence considers the logical and systematic relationships among various health outcomes that may be related to exposure. For example, the biologic mechanism underlying a reversible acute pulmonary function test reduction in children is most likely not part of the acute basis for a change in the mortality rate in adults. In assessing coherence, one should compare outcomes that look at similar time frames—daily hospitalizations compared to daily mortality rather than monthly hospitalizations.

There are now available a large number of community epidemiologic studies that specifically assess health effects of ambient exposure to at least one of the following four PM indicators: (1) thoracic PM ($PM_{10}$ or $PM_{15}$); (2) fine PM; (3) coarse PM; (4) sulfate and acid PM. Most of this body of indicator-specific evidence has appeared since the previous PM AQCD and promulgation of the U.S. EPA air quality standards for $PM_{10}$. To assist in the assessment of overall coherence across the relevant available epidemiologic database, it is helpful to summarize this evidence qualitatively.

Tables 13-6 and 13-7 present qualitative summaries of findings from community epidemiologic studies that specifically assess health effects of ambient exposure to one or more of the above four PM indicators. Table 13-6 summarizes findings on short-term exposure and table 13-7 summarizes findings on long-term PM exposure. For each PM indicator, the tables summarize findings for the health measures in the indicated population groups. The first step in preparing these tables was to develop separate layouts of cells for findings on short-term and long-term ambient PM exposures. The next step was to identify citations in the reference list of Chapter 12 that pertained to each individual cell. Community epidemiologic studies were included regardless of location and magnitude of ambient air pollution exposures. Review

articles, abstracts, and occupational studies were not included. For each table, all references used to derive the rating for each cell are presented in Appendix 13A.

Studies in which the analyzed PM exposure variable was TSP, BS, COH or some other PM surrogate were not included, unless gravimetric PM measurements had also been made in the study location which could serve as a basis for quantitative conversion to, or confident qualitative inference as to, levels of one or more of the PM indicators considered in these tables as per footnotes for each table.

Within each cell, the identified citations were qualitatively evaluated as a whole. In this evaluation, first consideration was given to the consistency of findings pertinent to a given cell. The following additional factors were also considered in this evaluation: (1) magnitude and statistical significance of observed effects estimates; (2) statistical power of study designs (dependent mainly on clarity of exposure-based comparisons, numbers of subjects, and durations of studies); and (3) pertinent information allowing reasonably confident relating of reported health effects to one or another of the specified PM indicators versus other pollutant measures.

Finally, each cell received a qualitative summary rating within the following 6-category scale: +++; ++; +; +/-; ID; and 0. This scale does not include a rating of "negative" because uniformly negative results were not observed in any cell for which pertinent studies were identified. The rating categories are described below.

| Rating | Description |
|---|---|
| +++ | Many studies identified and findings highly consistent across most or all studies, or fewer studies identified but findings highly reproducible and observed effects relatively large and statistically significant at $p \leq 0.05$. |
| ++ | Findings generally consistent across two or more studies and observed effects generally statistically significant, or relatively few studies identified and observed effects highly reproducible and statistically significant. |
| + | Findings somewhat mixed but generally consistent and at least some observed effects statistically significant, or few studies identified but incisive tests of effect were possible and results were generally statistically significant at $p \leq 0.05$. |
| +/- | Few pertinent studies identified, weight of evidence somewhat positive but uncertain. Usually at least one or more marginally significant ($p \leq 0.10$) PM-related effects reported. |

| | |
|---|---|
| ID | Insufficient data: at least 1 pertinent study identified but inference as to weight of evidence not warranted. |
| 0 | No pertinent studies identified. |

Tables 13-6 and 13-7 may be useful in providing the reader with an overview of the more specifically-targeted available epidemiologic studies, in assessing the relative health effects of specific components of the thoracic PM complex, in assessing the relative sensitivity of different subpopulations to ambient PM exposure, and in identifying needs for future epidemiologic research.

It is emphasized that Tables 13-6 and 13-7 are intended to assist in the overall evaluation of available epidemiologic evidence, not to substitute for it. The reader is strongly cautioned not to interpret these tables beyond their appropriate limits of inference. For example, these tables are silent with respect to many other epidemiologic studies of clear, continuing relevance in the PM risk assessment and risk management process, including important recent studies for which the sole PM exposure index was TSP and most other studies in which indices for ambient PM mass were not gravimetric measurements. These studies should be considered, together with the studies identified in tables 13-6 and 13-7, in assessing both the overall coherence of epidemiologic evidence and the potential public health consequences of ambient PM exposure.

Furthermore, the cell rating criteria did not include consistency of epidemiologic findings across different PM indices or other air pollutants, health indices, or population groups, or biological coherence of epidemiologic findings with experimental findings. Thus, these tables, alone, are not intended to yield conclusions bearing on important broader issues

## TABLE 13-6. QUALITATIVE SUMMARY OF COMMUNITY EPIDEMIOLOGIC FINDINGS ON SHORT-TERM EXPOSURE TO AMBIENT THORACIC PARTICLES AND SELECTED CONSTITUENTS

| | | Health Measure and Pollutant | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mortality | | | | Hospitalization and Outpatient Visits | | | | Community-Based Morbidity/Symptoms | | | | Changes in Lung Function | | | |
| Population Group | Subgroup | ThP | FP | CP[2] | $SO_4^=$ Acid | ThP | FP | CP[2] | $SO_4^=$ Acid | ThP | FP | CP[1] | $SO_4^=$ Acid | ThP | FP | CP[2] | $SO_4^=$ Acid |
| Adults | | | | | | | | | | | | | | | | | |
| | General Population | +++ | ++ | +/- | + | + | 0 | ID | 0 | +/- | 0 | 0 | +/- | + | 0* | 0 | 0 |
| | Elderly | + | + | 0 | 0 | ++ | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Respiratory[3] | ++ | + | 0 | 0 | ++ | +/- | ID | ++ | + | +✓ | 0 | + ✓ | 0 | 0 | 0 | 0 |
| | Cardiovascular | + | + | 0 | 0 | + | 0 | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Children | General Population | ID | 0 | 0 | 0 | + | 0 | ID | +/- | + | + | 0 | +/- | ++ | + | 0 | + |
| | Pre-existing Respiratory Conditions | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | +/- | 0 | +/- | + | ID | 0 | +/- |
| Asthmatics | Regardless of Age | 0 | 0 | 0 | 0 | ++ | +/- | +/- | + | + | +/- | ID | +/- | + | +/- | ID | +/- |

[1]FP = Indicator of fine-mode particles, usually $PM_{2.5}$, and ThP = Indicator of thoracic particles, typically $PM_{10}$.
[2]CP = Indicator of inhalable fraction of coarse-mode particles, usually ($PM_{10}$-$PM_{2.5}$) or ($PM_{15}$-$PM_{2.5}$).
[3]Respiratory causes of death.
[4]Cardiovascular causes of death.
ID = insufficient data, inference not warranted.
+/- = Few studies available, weight of evidence uncertain, but somewhat positive.
+ to +++ = Increasingly stronger, more consistent positive evidence for PM effects.
0 = No pertinent studies identified.
*Based on signficant positive association for Steubenville with CP found by Schwartz et al. (1966); but CP highly correlated with FP.
**CP not measured directly in Gordian et al. (1996) and/or Hefflin et al. (1994), but PM measured in CP-dominated polluted air.
✓ThP designation based on London BS having $D_{50}$ cut point = 4.5 that includes some ThP particles, but probably more closely indexed FP along with acid actually measured as $H_2SO_4$ in Lawther et al. (1970) study.

**TABLE 13-7. QUALITATIVE SUMMARY OF COMMUNITY EPIDEMIOLOGIC FINDINGS ON LONG-TERM EXPOSURE TO AMBIENT THORACIC PARTICLES AND SELECTED CONSTITUENTS**

| | | Health Measure and PM Indicator | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mortality | | | | Community-Based Morbidity/Symptoms | | | | Changes in Lung Function | | | |
| Population Group | Subgroup | ThP | FP | CP[2] | Acid-$SO_4^=$ | ThP | FP | CP[2] | Acid-$SO_4^=$ | ThP | FP | CP[2] | Acid-$SO_4^=$ [1] |
| Adults | General population | ++ | ++ | +/- | ++ | +/- | +/- | 0 | + | +/- | 0 | 0 | ID |
| | Elderly | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Cardiopulmonary[3] | ++ | +++ | 0 | ++ | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Children | General population | +/- | 0 | 0 | 0 | + | + | 0 | ++ | +/- | ID | 0 | + |
| Asthmatic-Atopic | Regardless of Age | 0 | 0 | 0 | 0 | + | +/- | 0 | +/- | 0 | 0 | 0 | 0 |

[1]FP = Indicator of fine-mode particles, usually $PM_{2.5}$.
[2]CP = Indicator of inhalable fraction of coarse-mode particles, usually ($PM_{10}$-$PM_{2.5}$) or ($PM_{15}$-$PM_{2.5}$).
[3]Combined cardiovascular and non-malignant respiratory causes of death.
0 = No pertinent studies identified.
ID = Insufficient data, inference not warranted.
[5]+/- = Few studies available, weight of evidence somewhat positive.
+ to +++ = Increasingly stronger, more consistent positive evidence for PM effect.
[*]Based on supplemental reanalysis by U.S. EPA of results from Dockery et al. (1993); see Figure 12-8 in Chapter 12.

such as biological plausibility of the epidemiologic findings or possible underlying mechanisms of action (which are discussed elsewhere in this chapter).

Within these important limitations, the tables suggest the following:

- Short-term exposure to ambient thoracic PM is consistently associated with adverse health effects ranging from mortality to changes in lung function. Long-term thoracic PM exposure is also strongly associated with increased mortality;
- Available evidence, though limited, suggests stronger associations of ambient fine PM exposure than coarse PM exposure with adverse health effects;
- The association of ambient PM exposure with total mortality is due primarily to its association with mortality due to respiratory and cardiovascular causes;
- There is reasonable consistency between findings on sulfate-acid exposure with findings on fine PM exposure. Because sulfates and airborne acid occur primarily in the fine PM fraction, this consistency reinforces observed associations of fine PM exposure with adverse health effects;
- Most available evidence regarding PM effects in adults comes from studies of mortality, hospitalization, and outpatient visits. Most evidence for children comes from community-based studies of morbidity, symptoms, and lung function. This impedes systematic assessment of the relative sensitivity of children and adults to ambient PM exposure;
- Very little is known about effects of long-term ambient PM exposure on chronic respiratory disease and stable lung function decrements in adults. Enhanced understanding in these areas will be especially important in assessing the biological coherence and credibility of observed associations of ambient PM exposure with increased mortality.

Table 3-8 provides further information indicative of quantitative coherence across several health endpoints, as observed in various PM epidemiology studies. The entries in the upper half of the table are for the whole population, including all age groups (designated as ALL). Overall, the data indicate that PM does have a relationship with a continuum of several health outcomes. Elevated mortality is the endpoint most clearly demonstrated to be affected in numerous studies, and represents the key endpoint for which coherence is sought in relation to other endpoints. The mortality studies suggest that mortality attributed to specific causes (respiratory,

cardiovascular) show stronger relationships (i.e., larger RR estimates) to PM measures than total mortality.

The health outcome potentially most related to cardiorespiratory mortality is hospital admissions for respiratory or cardiovascular causes in older age groups (i.e., > 65 years). In a qualitative sense, the increased mortality associated with ambient PM found in that age group should also be paralleled by increased hospital admissions within a similar time frame. Unfortunately, this issue has not been addressed specifically in relation to $PM_{10}$ exposures by those studies yielding the above results for the population as a whole. Information from other studies directly evaluating increased mortality and morbidity risk among the elderly in related to $PM_{10}$ measures is presented in the bottom half of Table 13-8.

A general way to assess quantitative coherence is to compare reported acute mortality and acute hospitalization risk estimates. One would expect that hospitalization would occur substantially more frequently than mortality, even though many deaths attributed to air pollution probably do not occur in hospital. Table 13-8 shows that this is indeed the case, using RR estimates developed in Chapter 12. For all age groups, expected respiratory mortality attributable to a 50 $\mu g/m^3$ increment in $PM_{10}$ is about 0.3 deaths per day per million people (based on analyses without copollutants at sites with 3 to 5 d averaging times), whereas 2.0 daily hospital admissions per million people for respiratory conditions attributable to $PM_{10}$ would be expected in the whole population. Similarly, 0.9 cardiovascular deaths per million per day can be projected to be associated with a 50 $\mu g/m^3$ increase in $PM_{10}$, compared to 2.3 hospital admissions for cardiovascular causes attributed to a comparable $PM_{10}$ increase. For age 65+, a total of 1.0 deaths per day from all causes attributed to $PM_{10}$ exposure might occur, whereas a larger number of daily hospital admissions would be expected for the two most common first-listed diagnoses, total respiratory conditions and heart disease. While there are some small numerical inconsistencies in Table 13-8, the coherence between the daily mortality results and the daily hospital admissions results is reassuring, considering the great diversity in study populations and analytical methods on which these estimates are based.

More specifically, we would expect 23.6 deaths per day per million people, of whom 17.0 would be age 65+ years, and 23.6 - 17.0 = 6.6 less than 65 years. Both the absolute number (17.0 per million) and the age-specific rate (17.0/126,000) are higher in the elderly.

## TABLE 13-8. QUANTITATIVE COHERENCE OF ACUTE MORTALITY AND HOSPITALIZATION STUDIES

| Age Group | Health Endpoint | Population Annual Baseline Per Million Total Population | Population Daily Baseline Per Million Total Population | $PM_{10}$ Lag Time | Excess Risk per 50 $\mu g/m^3$ $PM_{10}$ Incr. | Possible Number of PM-Related Events Per Day Per 1 Mil. Pop. for 50 $\mu g/m^3$ $PM_{10}$ Increment |
|---|---|---|---|---|---|---|
| Whole Population | | | | | | |
| All | Total mortality | 8,603[1] | 23.6 | <2d | 0.03[2] | 0.7 |
| | | | | 3-5d | 0.06[2] | 1.5 |
| | Total hospit. | 124,110[3] | 340.0 | - | - | - |
| All | Resp. mortality | 676[1] | 1.85 | 3-5d | 0.19[4] | 0.3 |
| | Total resp. hospitalization | 12,180[3] | 33.4 | <2d | 0.06[5] | 2.0 |
| All | Cardiovascular mortality | 3,635[1] | 10.0 | 3-5d | 0.09[4] | 0.9 |
| | Heart disease hospitalization | 21,310[3] | 58.4 | <2d | 0.04[6] | 2.3 |
| Elderly | | | | | | |
| 65+ | Total mortality | 6,201[7] | 17.0 | 2d | 0.06[8] | 1.0[8] |
| | Total hospit. | 42,845[9] | 117.4 | - | - | - |
| 65+ | Total resp. hospitalization | 5,101[9] | 14.0 | ≤1d | 0.08[5] | 1.1 |
| | Pneumonia hospit. | 2,335[9] | 6.4 | ≤1d | 0.08[10] | 0.5 |
| | COPD hospit. | 2,560[11] | 7.0 | ≤1d | 0.16[5] | 1.1 |
| | Heart disease hospitalization | 13,502[9] | 37.0 | ≤1d | 0.06[6] | 2.2 |

[1]From National Center for Health Statistics (1993).
[2]From EPA meta-analyses, Table 12-30, models without copollutants.
[3]From Table 12-6, based on first-listed diagnoses for discharges.
[4]From Pope et al. (1991), Schwartz (1993) for Utah Valley and Birmingham, variance-weighted average, Table 12-4.
[5]From Table 12-8, average.
[6]From Table 12-11.
[7]Assuming elderly as 12.6% of 1991 U.S. population.
[8]Based on different set of studies than for above whole population (ALL), i.e., 65+ PM mortality risk from Saldiva et al. (1994) and Ostro et al. (1996) variance-weighted average; Section 12.3.
[9]From Table 12-6, assuming 12.6%, age 65+.
[10]From Table 12-10, average.
[11]From 1992 detailed tables; excludes asthma (ICD 493).

The excess risk estimates for the elderly subpopulation and for the population as a whole are drawn from different studies in different communities, however, and therefore one should not expect complete consistency among estimates of excess mortality shown here to be attributable to an increment of 50 $\mu g/m^3$ $PM_{10}$. The expected number for the whole population, using the

short averaging time, is 0.03 (23.6) = 0.7 deaths per million, compared to 0.06 (17.0) = 1.0 deaths per million in the elderly. However, the difference of -0.3 is not attributable to beneficial effects of $PM_{10}$, but to uncertainty in the relative risk estimates and to the superposition of results from different studies; the difference is not statistically significant. The observation that there is not a significant excess of total deaths attributable to $PM_{10}$ beyond deaths of elderly people attributable to $PM_{10}$ suggests that the number of deaths in younger people attributable to $PM_{10}$ is relatively small. There have been few efforts to establish age-specific PM mortality rates, however, (Lyon et al., 1995)
with a little evidence for excess mortality in young children. Some studies for TSP suggest little excess mortality for young adults (Schwartz, 1994b; Wyzga and Lipfert, 1995) and increasing attributable excess risk with increasing age.

The element of coherence is further strengthened by those studies in which increased frequency of different health outcomes associated with PM are found in the same population. If the PM effect on mortality and hospitalization were real, we would expect to observe PM-associated mortality and hospitalization from the same conditions in the same populations. This has indeed been observed in several populations, as summarized below:

- Detroit: Mortality mainly in elderly populations, hospital admissions for respiratory causes and for cardiovascular causes in the elderly;
- Birmingham: Mortality mainly in the elderly, hospital admissions for the elderly;
- Philadelphia: Mortality and hospital admissions for pneumonia in the elderly;
- Utah Valley: Mortality and hospital admissions for respiratory causes in adults.

In the latter study, in addition to hospital admissions, other outcomes were associated with PM episodes including decrements in peak flow, increased respiratory symptoms and medication use in asthmatics, and elementary school absences. The presence of a primarily non-smoking population more or less eliminates smoking as a source of confounding. While these multiple outcomes did not occur in strictly identical subgroups of each population, there was probably a sufficient degree of overlap to indicate that PM was a significant predictor of a broad range of related health outcomes within this community. Significant decrements in pulmonary function and increased incidence of symptoms were associated with daily increases in PM in children in Utah Valley, along with a "quality of life" effect measured by lost school days. Thus, there is evidence for increased risk of health effects associated with PM exposure that range in severity

from asymptomatic pulmonary function decrements, to respiratory and cardiopulmonary illness requiring hospitalization, to excess mortality from respiratory and cardiovascular causes, especially in those older than 65 years of age.

## 13.5 POTENTIAL MECHANISMS AND EFFECTS OF SELECTED PM CONSTITUENTS

Epidemiologic studies have suggested that ambient particulate exposure may be associated with increased mortality and morbidity at PM concentrations below those previously thought to affect human health (Chapter 12). This section discusses the nature of observed effects reported in the above-discussed epidemiologic observational studies and attempts to interrelate such findings to available supporting information on hypothesized potential mechanisms of action that might contribute to increased human morbidity and mortality. Also discussed is information from limited controlled human and laboratory animal studies pertaining to identification of specific ambient PM constituents as possible etiologic contributors to reported ambient PM effects.

### 13.5.1 Characteristics of Observed Morbidity and Mortality

To approach the difficult problem of determining if the association between low-level PM concentrations and daily morbidity and mortality is biologically plausible, one must consider: the chemical and physical characteristics of the particles in the inhaled atmospheres; the characteristics of the morbidity/mortality observed and the affected population; as well as potential mechanisms that might link the two. Several salient considerations related to the evaluation of biological plausibility of the epidemiology findings are discussed below.

If daily mortality rates are associated with elevated ambient particulate concentrations, it is important to examine the specific causes of death to determine if they could plausibly be contributed to by inhaled PM. Schwartz (1994b,c) compared causes of death in Philadelphia on high pollution days (average TSP = 141 $\mu g/m^3$) with causes of deaths on lower pollution days (average TSP = 47 $\mu g/m^3$). On the high pollution days there was a higher relative increase in deaths due to: COPD (RR = 1.25); pneumonia (RR = 1.13); cardiovascular disease (RR = 1.09); and stroke (RR = 1.15). There was also a higher relative age at death and an increase in reports

that respiratory factors may have contributed to the cause of death. The causes of death and age at death were found to be similar to those observed in the London smog deaths of 1952.

Studies of associations of morbidity with particulate pollution noted small decreases (2 to 2.5%) in spirometry (FVC or $FEV_1$) in smokers and nonsmokers on high pollution days (60 to 100 µg/$m^3$; Pope and Kanner, 1993; Chestnut et al., 1991), an increased number of asthma attacks (Pönkä, 1991), and increased outpatient visits for asthma (Gordian et al., 1996) and bronchitis (but not for asthma) (Hefflin et al., 1994). Thus, the characteristics of health effects on high particle pollution days are mainly cardiopulmonary in nature and are the types of effects that can be considered plausibly related to airborne toxicants.

Data on the lung function effects of particle exposures in persons with pre-existing pulmonary disease compared to healthy persons do not yield a clear picture although they are logically likely to be more susceptible to effects from exposure to particulate pollutants. Pope and Kanner (1993) reported an approximate 2% decline in $FEV_1$ in smokers with mild to moderate COPD during an increased concentration in ambient $PM_{10}$ of 100 $\mu$g/$m^3$ in Salt Lake City. However, in controlled exposures to similar concentrations of $H_2SO_4$, persons with mild COPD (average $FEV_1$/FVC ratio 56%) had no reduction in spirometry (Morrow et al., 1994). Exercising mild asthmatics may (Morrow et al., 1994; Koenig et al., 1989) or may not (Avol et al., 1990) experience slight bronchoconstriction following similar acid aerosol exposures. Using an elastase-induced rat model of emphysema, Mauderly et al. (1990) found that exposure to diesel exhaust, which contains aggregates of ultrafine soot particles, resulted in less particle deposition in the lungs of emphysematous rats than in normal rats, thus sparing the emphysematous rats the health effects induced by the soot particles in normal animals.

A portion of PM-related deaths may occur during short-term ambient PM episodes in persons who would have died within days or weeks. For this portion, a "harvesting effect" would logically be expected in the daily mortality statistics. That is, after the episode-related increase in mortality, the daily mortality count should decline below baseline, because some of those at risk would already have died. This decline would be expected within the period of PM-induced life shortening.

Kunst et al. (1993) have reported a harvesting effect with temperature-related mortality, and some epidemiologic studies (Cifuentes and Lave, 1996 and Spix et al., 1993) have reported such effects to be associated with episodic ambient PM exposure. Even if true PM-related

harvesting exists, epidemiologic studies may generally not be sensitive enough to detect it, because the PM effect on overall mortality is relatively small, and because it is likely that multiple mechanisms with variable time courses are involved in PM-related mortality. For example, in the 1952 London fog episode, daily mortality did not quickly return to baseline following the peak in excess deaths. Rather, mortality remained somewhat elevated in the days after pollution levels had returned to baseline (Logan, 1953). This observation suggests that among the deaths associated with short-term ambient PM exposure, the time of life lost is variable.

Particle exposure could conceivably increase susceptibility to infection with bacteria or respiratory viruses, leading to an increased incidence of respiratory infections such as pneumonia in susceptible members of the population. Potential mechanisms could include slowing of mucociliary clearance, impairment of alveolar macrophage function, and other specific or nonspecific effects on the immune response. Incubation periods for common pneumonias are in the range of 1 to 3 days although some forms require substantially longer (Benenson, 1990) and the relative risk of death from pneumonia was positively associated with ambient PM in Philadelphia. If pollutant exposure increased susceptibility to infectious disease, it might be possible to detect differences in the incidence of such diseases in communities with low versus high PM concentrations (Utell and Framptom, 1995). If so, emergency room visits and hospitalizations for pneumonia caused by the relevant agent could be measurably higher on days following elevated ambient particle concentrations. Schwartz (1994a,b) reported increased risk (RR 1.19; 95% CI, 1.07 to 1.32) for pneumonia hospitalization associated with $PM_{10}$ (100 $\mu g/m^3$) in Birmingham for patients aged 65 and older. On the other hand, although bronchitis and asthma admissions for children were increased approximately twofold in association with operation of a steel mill in the Utah valley, pneumonia admissions for all ages were not increased. Laboratory animal data to support a direct causal link between PM exposure and death induced by pneumonia pathogens are not available. Although exposure to acidic aerosols has been linked with alterations in mucociliary clearance, non-acidic aerosols and other PM species have not been shown experimentally to cause increased susceptibility to infection in otherwise healthy young animals. Infectivity studies in old animals, as models of chronic respiratory disease, could be potentially instructive in this regard.

Particulate air pollution might also aggravate the severity of underlying chronic lung disease. This mechanism could explain increases in daily mortality and longitudinal increases in mortality if individuals with chronic airways disease experienced more frequent or severe exacerbation of their disease, or more rapid loss of function as a result of particulate exposure. If so, increased hospital admissions for specific respiratory causes should be associated with PM. There are numerous examples (cited in Chap. 12) of increased hospital admissions for COPD, bronchitis, and asthma being associated with variations in PM levels.

### 13.5.2 Possible Mechanisms of PM-Induced Injury

Several potential pathophysiologic mechanisms can be proposed by which low level ambient particle concentrations could conceivably contribute to morbidity and mortality. As discussed in Chapter 11, PM has been identified as causing a variety of health effects including respiratory symptoms, mechanical changes in lung function, alteration of mucociliary clearance, pulmonary inflammatory responses and morphological alterations in the lung. In addition, PM has been associated with respiratory illness, hospital admissions, and increased daily mortality.

In this section, attention is directed at pulmonary and cardiovascular mechanisms which could hypothetically contribute to increased morbidity and mortality, although it is acknowledged that specific mechanisms of action for PM are not yet well known. The phenomenon of particle related mortality may include: (1) "premature" death (or mortality displacement), that is the hastening of death for individuals already near death (i.e., hastening of certain death by hours or days); (2) increased susceptibility to infectious disease; and (3) exacerbation of chronic underlying cardiac or pulmonary disease (Utell and Frampton; 1995). The distribution of deposition of particles inhaled into the respiratory tract depends on their size, shape, chemical composition, and the airway geometry and pulmonary ventilation characteristics of the organism. The mechanisms responsible for the broad range of particle-related health affects will vary depending on the site of deposition. Once deposited, the particles may be cleared from the lung, translocated into the interstitium, sequestered in the lymph nodes, metabolized or otherwise transformed by mechanisms described in Chapter 10.

Deposition of particulate matter in the human respiratory tract could initiate events leading to increased airflow obstruction, impaired clearance, impaired host defenses, or increased epithelial permeability. Airflow obstruction could result from laryngeal constriction or

bronchoconstriction secondary to stimulation of receptors in extrathoracic or intrathoracic airways. In addition to reflex airway narrowing, reflex or local stimulation of mucus secretion could lead to mucus hypersecretion and could eventually contribute to mucus plugging in small airways. Finally, in airways disease with localized airway narrowing or obstruction, PM will tend to accumulate more rapidly.

One component of PM, namely acid aerosols, is known to cause slowing of mucociliary clearance. Since this mechanism is important in clearing particles from the lung, including biologically active particles such as spores, fungi, and bacteria, impairment of mucociliary clearance could lead to increased PM burdens, inflammation, and infection. Alveolar clearance may also be impaired through alterations in macrophage function including decreased phagocytosis, depression of mobility, and decreased adherence to surfaces. Macrophages play an important role in removing and digesting particles and may be involved in facilitating translocation of PM to either other parts of the lung or into the vascular system.

PM may transport reactive oxygen species or increase their formation. PM may induce or enhance an inflammatory response in the lung; such an effect may depend on particle size and hence deposition site as well as on chemical or biological composition of the particles. Inflammatory responses can lead to increased permeability and possibly diffusion abnormality. Retention of PM may be associated with the initiation and/or progression of COPD. In addition, mediators released during an inflammatory response could cause release of factors in the clotting cascade that may lead to an increased risk of thrombus formation in the vascular system (Seaton et al., 1995).

Pulmonary changes that contribute to cardiovascular responses include a variety of mechanisms which can lead to hypoxemia, including bronchoconstriction, apnea, impaired diffusion, and production of inflammatory mediators. Hypoxia can lead to cardiac arrhythmias and other cardiac electrophysiologic responses that in turn may lead to ventricular fibrillation and ultimately cardiac arrest. Additionally, many respiratory receptors have direct cardiovascular effects. Stimulation of C-fibers leads to bradycardia and hypertension, while stimulation of laryngeal receptors can result in hypertension, cardiac arrhythmia, bradycardia, apnea, and even cardiac arrest. Nasal receptor or pulmonary J-receptor stimulation can lead to vagally mediated bradycardia and hypertension (Widdicombe, 1988). Unfortunately, little is known about the effects of aging on airway receptor reflexes and their cardiac effects, and

limited research evaluating potential triggering of terminal cardiac events (e.g., arrhythmias) by inhaled ambient PM is only now beginning to yield preliminary results.

In addition to possible acute toxicity of particles in the respiratory tract, particles that deposit in the lung may induce inflammation. The response of the respiratory tract to such particles includes the release of numerous cytokines from alveolar macrophages and epithelial lining cells that promote healing and repair. With repeated cycles of acute lung injury and repair or with the persistence of toxic particles chronic lung injury could develop. Although such acute responses are well known, they typically occur only after several days or weeks of exposure to airborne particle concentrations many fold higher than those ambient exposures that have been shown to be associated with increased mortality and morbidity in epidemiology studies.

### 13.5.3 Specific PM Constituents: Acid Aerosols

Acid aerosol exposure in controlled human exposure and laboratory animal toxicology studies has been shown to cause a variety of effects on the respiratory system. In humans acutely exposed to acid aerosols, these include decrements in lung function, slowing of mucociliary clearance, and increased airway responsiveness and respiratory symptoms.

Human experimental studies indicate that healthy subjects experience only very modest decrements in respiratory mechanics following single exposures to $H_2SO_4$ at levels up to 2,000 $\mu g/m^3$ for 1 h. Acid aerosol deposition and neutralization models suggest that with the ammonia present in the mouth and respiratory tract of humans, a large portion of inhaled acids will be neutralized during inhalation. Nevertheless, even with exercise to decrease the time for neutralization and the use of acidic gargles to minimize the levels of oral ammonia available for neutralization, lung function and symptom responses are not appreciably enhanced in healthy subjects. Mild lower respiratory symptoms occur at exposure concentrations in the >1,000 $\mu g/m^3$ range, particularly with larger particle sizes. These observations are consistent with deposition models that indicate greater deposition of larger aerosols in the tracheobronchial region, the origin of many of the respiratory symptoms such as cough and irritation. However, these observations do not provide an explanation for the observed lower levels of FVC and $FEV_1$ seen in children who reside in communities with high levels of acidic PM. The only studies of controlled acid exposures in non-adults are those of adolescent asthmatics, discussed below.

Both acute and chronic exposure to $H_2SO_4$ can produce functional changes in the respiratory tract, some of which have a greater pathological significance than others. Acute exposure will alter pulmonary function, largely due to bronchoconstriction. However, attempts to produce changes in airway resistance in healthy animals at levels below 1,000 $\mu g/m^3$ have been largely unsuccessful. With the exception of guinea pigs, these findings in laboratory animals are similar to those for healthy humans. The lowest effective level of $H_2SO_4$ producing a small transient change in airway resistance in the guinea pig is 100 $\mu g/m^3$ (1-h exposure). In general, the smaller size droplets were more effective in altering pulmonary function, especially at low concentrations. Deposition models predict that only smaller aerosols (< 2-4 $\mu m$) would have appreciable tracheobronchial and alveolar deposition in small laboratory animals. Chronic exposure to $H_2SO_4$ is also associated with alterations in pulmonary function (e.g., changes in the distribution of ventilation and in respiratory rate in monkeys). However, in these cases the effective concentrations are $\geq 500$ $\mu g/m^3$. Hyperresponsive airways have been induced with repeated exposures to 250 $\mu g/m^3$ $H_2SO_4$ in rabbits. Acute exposures to higher concentrations did not affect responsiveness in healthy humans but exposures in the 500 to 1,000 $\mu g/m^3$ range in asthmatics can result in changes in airway responsiveness. Because droplet aerosols are highly soluble, it is unlikely that any appreciable lung burden of these particles would accumulate.

Asthmatic subjects appear to be more sensitive than healthy subjects to the effects of acid aerosols on lung function, but the effective concentration differs widely among studies. Adolescent asthmatics may be more sensitive than adults, and may experience small decrements in lung function in response to $H_2SO_4$ at exposure levels only slightly above peak ambient levels. Mild bronchoconstriction has been reported after brief exposures to as low as 68 $\mu g/m^3$ $H_2SO_4$ in exercising adolescent asthmatics and 90 $\mu g/m^3$ in exercising adult asthmatics (Morrow et al., 1994; Koenig et al., 1989), although this has not always been observed (Avol, et al., 1990). These observations may be consistent with the association of pulmonary function decrements with acidic PM exposure in children attending summer camps. Acid aerosol probably acts as an irritant in the tracheobronchial region and increased responsiveness in this region is the likely cause of increased response of asthmatics to acids. If chronic acid exposure were to exacerbate asthma in children, this could partially account for the reduced lung function levels found in communities with higher levels of acidic PM. In very limited studies, the elderly and people

with COPD do not appear to be unusually susceptible to the effects of acid aerosols on lung function.

Acid aerosols typically cause slowing of mucociliary clearance in healthy subjects, although the effects are dependent on exposure concentration and exposure duration and on the region of the lung being studied (brief exposure to low concentrations of acid may accelerate clearance of particles deposited primarily in the tracheobronchial region). The bronchial mucociliary clearance system in laboratory animals is also very sensitive to inhaled acids. The lowest level shown to have an effect on mucociliary transport rates in healthy laboratory animals (100 $\mu g/m^3$ with repeated exposures) is well below that which results in other physiological changes in most laboratory animals and is consistent with the findings in humans exposed to acid aerosols.

The lungs have an array of defense mechanisms to detoxify and physically remove inhaled material, and available evidence indicates that certain of these defenses may be altered by exposure to $H_2SO_4$ levels <1,000 $\mu g/m^3$. Defenses such as resistance to bacterial infection may be altered even by acute exposure to concentrations of $H_2SO_4$ around 1,000 $\mu g/m^3$. Limited data also suggest that exposure to acid aerosols may affect the functioning of alveolar macrophages at levels as low as 500 $\mu g/m^3$ $H_2SO_4$. However, in humans, exposure to acid aerosol (1,000 $\mu g/m^3$) did not appear to induce an inflammatory response or to cause any changes in macrophage function (Frampton et al., 1992). Alveolar region particle clearance is affected by repeated $H_2SO_4$ exposures to as low as 125 $\mu g/m^3$, although these are still higher than currently observed ambient acid U.S. concentrations. One would expect effects from impaired pulmonary defense mechanisms to develop over an extended period of continuing exposure. Impairment of pulmonary host defense mechanisms by acidic particles is consistent with the observations of increased prevalence of bronchitis in communities with higher levels of acidic PM.

The assessment of the toxicology of acid aerosols requires some examination of potential interactions with other air pollutants. Such interactions may be antagonistic, additive, or synergistic. Evidence for interactive effects may depend upon the sequence of exposure as well as on the endpoint examined. Low levels of $H_2SO_4$ (40 to 100 $\mu g/m^3$) have been shown to react synergistically with $O_3$ in simultaneous exposures using biochemical endpoints. In this case, the $H_2SO_4$ enhanced the damage due to the $O_3$. Two recent studies have examined the effects of exposure to both $H_2SO_4$ and ozone on lung function in healthy and asthmatic subjects. In

contrast with several previous studies conducted at higher acid concentrations, both studies suggested that 100 $\mu g/m^3$ $H_2SO_4$ may cause slight potentiation of the pulmonary function response to ozone.

The surface of a particle is primarily in contact with respiratory cells and surfaces and thus any coating on a solid particle, such as acid, would be presented to the respiratory surfaces. Acid coating of ultrafine zinc oxide particles appears to enhance the effects of acid in the guinea pig, for both permeability, inflammation, and some functional responses such as changes in diffusing capacity (Chen et al., 1992; 1995). However, acid coating of fine (<1 $\mu$m) carbon particles did not enhance the responses of humans to acid aerosols (Anderson et al., 1992). The process of acid coating used by Anderson et al. (1992) is different form that used by Chen et al. (1995) and these data may not be comparable. It is unclear whether these differences can be attributed to the acid coating alone since the carrier particle (ZnO versus C) may play a role and, in the case of the ultrafine coated particles, the total number of particles *per se* may play a role in the response. Moreover, Chen et al. (1995) noted changes in intracellular pH of macrophages, which may affect phagocytosis, following exposure to aerosols of $H_2SO_4$ layered on carbon particles. This effect was dependant both upon the number of particles as well as the total mass concentration of $H^+$ in the exposure atmosphere; a threshold existed for both exposure parameters. Similar amounts of (larger) droplet acid aerosol did not produce these responses in guinea pigs. This latter

finding is consistent with a single human study of very fine acid/sulfate particle exposure in which no spirometry responses were observed at levels in excess of 1000 µg/m$^3$ (Horvath et al., 1987).

Human exposure studies of particles other than acid aerosols provide insufficient data to draw conclusions regarding health effects. However, available data suggest that inhalation of inert particles in the respirable range, including three studies of carbon particles, have little or no effect on symptoms or lung function in healthy subjects. Although, coating of micron-sized carbon particles with sulfuric acid did not increase pulmonary function responses, carbon particles impregnated with formaldehyde did increase the delivery of formaldehyde and consequently increased irritant responses in human subjects.

### 13.5.4 Specific PM Constituents: Ultrafine Aerosols

Ultrafine aerosols (<0.1 $\mu$m) are a class of particles that have the potential to cause toxic injury to the respiratory tract as seen in studies conducted both in vivo and in vitro. At high concentrations, ultrafine particles, as a metal or polymer "fume", are associated with toxic respiratory responses both in humans and in laboratory animals. Occupational exposures to high levels of polymer fumes (>1,000 $\mu$g/m$^3$; size <1 $\mu$m) can lead to fever, diffusion impairment, and respiratory symptoms (Dahlqvist et al., 1992; Goldstein et al., 1987). Such exposures are associated with cough, dyspnea, pulmonary edema, and acute inflammation.

Ultrafine (11 nm) particles of copper oxide inhaled at $10^9$ particles/cm$^3$ for 60 minutes in hamsters were dispersed throughout the lung including the interstitium, the alveolar capillaries and the pulmonary lymphatics (Stearns et al., 1994). During the exposure pulmonary resistance increased four-fold and the increase persisted for 24 h. These results indicate that ultrafine particles of low solubility can rapidly breach epithelial cell barriers and penetrate to interstitial and endothelial sites.

The potential for toxicity of ultrafine particles has been studied using a polymer ultrafine particle as a model (Oberdörster et al., 1995a,b; Warheit et al., 1990). These studies indicate that freshly generated insoluble ultrafine particles, when inhaled as single particles in low concentrations (<50 $\mu$g/m$^3$) can cause severe injury to the lung. In addition there are studies on a number of relatively insoluble ultrafine particles (diesel, carbon black) that are present in the ambient atmosphere as aggregated ultrafines. These studies, reviewed in Chapter 11, indicate

that inhalation exposures of laboratory animals to aggregated particles, including $TiO_2$, carbon black particles and diesel soot are associated with epithelial cell proliferation, occlusion of interalveolar pores (of Kohn), impairment of alveolar macrophages, chronic pulmonary inflammation, pulmonary fibrosis, and induction of lung tumors. No acute effects were observed, however, even at the highest exposure concentrations.

As reviewed in Chapter 11, mechanisms which could enhance the toxicity of ultrafine particles include: the high pulmonary deposition efficiencies of inhaled singlet ultrafine particles; the large numbers of these particles per unit mass; their increased surface area available for reaction; their rapid penetration of epithelial layers and access to pulmonary interstitial sites; and the presence of radicals and perhaps acids on the particle surface. When inhaled at the same mass concentration, ultrafine particles with a diameter of 20 nm have a number concentration that is approximately 6 orders of magnitude higher than for a 2.5 µm particle; the collective particle surface area is also greatly increased (Table 11-1) Ultrafine particles present a problem to the respiratory tract because of their large collective surface area and because they can evade macrophage phagocytosis and penetrate into the interstitium more easily than larger sized particles (Takenaka et al., 1986; Ferin et al., 1990). There is evidence that some aggregated insoluble ultrafine particles may dissociate into singlet ultrafine particles in the lung (Takenaka et al., 1986; Ferin et al., 1990; Oberdorster, et al., 1994) which would facilitate transport across the epithelium. Even though the deposition of aggregated ultrafines would be similar to particles in the fine range, their behavior in the lung would be that of singlet ultrafine particles.

The occurrence of ultrafine particles as well as their sources are reviewed in Chapters 3 and 6. Single ultrafine particles occur regularly in the urban atmosphere at high number concentrations ($5 \times 10^4$ - $3 \times 10^5$ particles/$cm^3$) but very low mass concentrations (Brand et al., 1991; 1992; Castellani, 1993). Particle number concentrations may vary from less than 1000/$cm^3$ at clean, background sites to over 100,000 $cm^3$ in polluted urban areas. Geometric mean diameter ranged from 12 to 43 nm in Long Beach, CA and 47 to 75 nm in clean air in the Rocky Mountains. Although ultrafine particles are not stable because they quickly aggregate to form larger particles, they continue to be freshly generated from a number of anthropogenic sources (e.g., gas to particle conversion; combustion processes; incinerator emissions). Moreover, the presence of ultrafine particles in human alveolar macrophages indicates

widespread exposures to ultrafines, either as singlet particles or aggregates in ambient air (Hatch et al., 1994).

At present there are no studies with ambient ultrafine particles. An important aspect of the potential toxicity of ultrafine particles is their low solubility whether they are present in the exposure atmosphere as singlet particles or as aggregates. At this point the limited data base does not permit a judgment to be made on the potential for ultrafine particles to contribute to morbidity and/or mortality consistent with the epidemiologic findings for ambient particle exposures.

### 13.5.5 Specific PM Constituents: Crystalline Silica

The limited data on air concentrations of silica in the United States indicate that silica particles arising from natural, industrial, and farming activities can result in estimated ambient annual average and high ambient quartz levels of 3 and 8 $\mu g/m^3$, respectively. However, silica is one of the most common substances to which workers are exposed and several extensive occupational studies clearly define the exposure levels and resultant health effects. Consequently, a causal relationship between inhalation of dust containing crystalline silica and pulmonary inflammation and the consequent development of fibrosis (silicosis) is well-established. Although a correlation between silicosis and increased risk of neoplasia is suggested by the results of recent occupational studies, experimental evidence that quartz can cause lung cancer without silicosis, has only been seen in rats. Rats appear to be more sensitive to the development of silica-induced lung injury and lung tumors than other rodent species such as mice and hamsters. Although the pulmonary pathological effects of inhaled crystalline silica are well-established, there is little information on the effects of inhaled amorphous silica. The limited information suggests that, in the absence of continuing exposures, the respiratory tract effects following exposures to amorphous silicates are reversible, and occur only in laboratory animals exposed to silica in excess of 10,000 $\mu g/m^3$ for periods ranging from days to years. The results demonstrate that the crystalline forms of silica dust were substantially more potent in producing pulmonary toxicity compared to the amorphous or colloidal forms of silica. Differences in sensitivity to inhaled silica are apparent not only across and within rodent species, but also between rodents and humans; this limits the utility of laboratory animal data for extrapolation of silica risk to ambient level exposures.

The effects of crystalline silica exposure (CSE) have been extensively studied in mining environments, and there are some clear differences between the mining environments and the ambient environment. These differences generally suggest that silica in the ambient environment is less toxic, primarily because of the larger particle sizes associated with ambient sources, the reduced likelihood of exposure to more potent "freshly fractured" silica, and less frequent peak exposures. In any case, a thorough analysis of the most extensive occupational studies available, each of which examined the medical histories of thousands of miners, suggests that the cumulative risk of silicosis among South Dakotan, Canadian, and South African miners from exposures at or below 1000 $\mu$g crystalline silica/m$^3$ · years is very nearly 0%. Using a high estimate of 10% for the crystalline silica fraction in $PM_{10}$ from U.S. metropolitan areas, 1000 $\mu$g crystalline silica/m$^3$ · years is the highest CSE expected from continuous lifetime exposure at or below the annual $PM_{10}$ NAAQS of 50 $\mu$g/m$^3$. Thus, current data suggest that, for healthy individuals not compromised by other respiratory ailments and for ambient environments expected to contain 10% or less crystalline silica fraction in $PM_{10}$, maintenance of the 50 $\mu$g/m$^3$ annual NAAQS for $PM_{10}$ would be adequate to protect against silicotic effects from ambient crystalline silica exposures.

### 13.5.6 Specific PM Constituents: Bioaerosols

Ambient bioaerosols include fungal spores, pollen, bacteria, viruses, endotoxin, and animal and plant debris. Bacteria, viruses and endotoxin are mainly found attached to aerosol particles, while entities in the other categories are found as separate particles. Data for characterizing ambient concentrations and size distributions of bioaerosols are sparse. Matthias-Maser and Jaenicke (1994) found that bioaerosols constituted about 30% of the total number of particles in samples collected on a clean day in Mainz, Germany. The proportion of particles that were bioaerosols was higher in the fine size mode (as much as a third) and slightly lower in the coarse size mode. In Brisbane, Australia, Glikson et al. (1995) found that fungal spores dominate the bioaerosol count in the coarse fraction of $PM_{10}$ and that the overall contribution of bioaerosols to total $PM_{10}$ particulate mass was on the order of 5 to 10%. However, the cytoplasmic content of spores and pollen was often found to be adhered to particles emitted by motor vehicles and particles of crustal origin.

Fungal spores range in size from 1.5 µm to >100 µm, although most are 2 to 4 µm MMAD. They form the largest and most consistently present component of biological aerosols in ambient air. Levels vary seasonally, usually being lowest when snow is on the ground. Fungal spores often reach levels of 1000 to 10,000 spores/$m^3$ during the summer months (Lacey and Dutkiewicz, 1994; Madelin, 1994) and may be as high as 100,000/$m^3$ near some anthropogenic sources (agriculture activities, compost, etc.).

Bioaerosols can contribute to increased mortality and morbidity. Asthma mortality has been associated with ambient levels of fungal spores, unadjusted OR of 2.16 (95% CI = 1.31 to 3.56) per increment of 1000 spores/$m^3$; controlling for time and pollen counts reduced the RR to 1.2 (95% CI = 1.07 to 1.34) (Targonski et al., 1995). Asthma mortality in Scotland shows a seasonal peak that follows the peak in ambient pollen levels (Mackay et al., 1992). Exposure to fungal spores has also been identified as a possible precipitating factor in respiratory arrest in asthmatics (O'Hollaren et al., 1991).

Exposure to fungal spores in healthy individuals can lead to allergic alveolitis (hypersensitivity pneumonitis) or pulmonary mycoses such as coccidioidomycosis or histoplasmosis (Lacey and Dutkiewicz, 1994). Induction of hypersensitivity generally requires exposure to concentrations that are substantially higher than in ambient air, although subsequent antigenic responses require much lower concentrations. Association of fungal and pollen spores with exacerbations of asthma or allergic rhinits is well established (Ayres, 1986). The incidence of many other diseases (e.g., coccidioidomycosis) induced by fungal spores is relatively low, although there is no doubt about the causal organisms (Lacey and Dutkiewicz, 1994). The potential for fungal induced diseases is much higher in immunocompromised patients and those with unusually high exposures to crustal dust in the breathing zone, such as military personnel.

In addition to fungal spores and pollen, other bioaerosol material can exacerbate asthma and can also induce responses in nonasthmatics. For example, in grain workers who experience symptoms, spirometry decrements, and airway hyperresponsiveness in response to breathing grain dust, the severity of responses is associated with levels of endotoxin in the bioaerosol rather than the total dust concentration (Schwartz et al., 1995). A classic series of studies (Antó and Sunyer, 1990) proved that airborne dust from soybean husks was responsible for asthma epidemics and increased emergency room visits in Barcelona, Spain. These studies indicate that airborne fragments of biological substances can produce severe health effects.

Bacterial aerosol counts may range as high as 30,000 bacteria/$m^3$ downwind of sewage treatment facilities, composting areas, waterfalls from polluted rivers, or certain agricultural activities. Typical levels in urban areas range from several hundred to several thousand bacteria/$m^3$ (Lighthart and Mohr, 1994). Human pathogenic activity of such bacteria is not well understood or characterized. Infective potential of aerosolized bacteria depends on size (smaller are more effective), virulence, host immune status, and host species sensitivity (Salem and Gardner, 1994). Aerosolized bacteria can cause bacterial infections of the lung including tuberculosis and legionnaire's disease. The *Legionella pneumophila* bacterium is one of the few infectious agents known to reside outside an infected host and is commonly found in water, including lakes and streams. Levels of bioaerosols (fungi and bacteria) are generally higher in urban than in rural areas (Lighthart and Stetzenbach, 1994).

Exposures to bioaerosols of the above types, are clearly capable of producing serious health effects especially at high concentrations encountered in indoor environments.

Because of the extremely limited knowledge of ambient levels of bioaerosols and their composition and relative potency of various components, the small number of well conducted epidemiologic studies of bioaerosols, and the absence of controlled studies of ambient bioaerosols, the relative contribution of bioaerosols to the observed PM-associated morbidity and mortality effects cannot be determined with any confidence at the present time. However, it seems unlikely that bioaerosols play more than a minor role in such effects. This conclusion is based on

1. The seasonal variability in concentration of some bioaerosols whose general trends are different from the seasonal trends in mortality.
2. The subpopulation most afflicted by bioaersols is asthmatics who are not identified as a sensitive subgroup for PM-associated mortality.
3. Many of the specific diseases induced by bioaerosols have an extremely low incidence and, for many, the mortality rate is also very low.

## 13.6 INDIVIDUAL RISK FACTORS AND POTENTIALLY SUSCEPTIBLE SUBPOPULATIONS

In addition to risk associated with activity, location, and dosimetry, inherent individual characteristics may also affect risk from inhaled PM. For example, elderly individuals or persons with pre-existing cardiovascular or respiratory disease, particularly chronic obstructive pulmonary disease (COPD), are likely to be at greater risk from PM exposure. Both the incidence of and the death rates from cardiovascular and pulmonary diseases increase with age. The following section discusses individual risk factors, including: age, asthma, COPD, and cardiovascular disease. The incidence of selected cardiopulmonary diseases by age and geographic region is presented in Table 13-9 to help place the following discussion in perspective.

### 13.6.1 Age

Certain population groups such as the elderly may be more sensitive to changes in pulmonary or cardiovascular function because of age-related decrements in physiological reserve. For example, cardiorespiratory function, including lung volumes, $FEV_1$, maximum oxygen uptake, and cardiac output reserve decline with age (Folkow and Svanborg, 1993; Dice, 1993; Lakatta, 1993; Kenney, 1989), even in a healthy active population. Morphological changes in the lung lead to loss of lung elasticity, increased stiffness of the chest wall, enlargement of alveolar ducts and loss of alveolar septa including diminished numbers of pulmonary capillaries, and increased numbers of mucous glands. Many of the decrements in physiological function associated with the aging process also may be associated with pathological changes caused by disease or other environmental stressors impacting a person over their lifespan.

If the pulmonary clearance mechanisms are impaired due to pulmonary disease, aging, or repeated inhalation exposures that are toxic to the normal clearance mechanisms, then particles and their metabolic or degradation products may persist. The degree to which an added particle burden may impact an individual will likely be affected by their age, health status, medication usage and their overall susceptibility to this inhalation exposure. One factor that may promote increased risk in the older population is that, over their lifespan,

## TABLE 13-9. INCIDENCE OF SELECTED CARDIORESPIRATORY DISORDERS BY AGE AND BY GEOGRAPHIC REGION (reported as incidence per thousand population and as number of cases in thousands)

| | | Age | | | | Regional | | | |
|---|---|---|---|---|---|---|---|---|---|
| Chronic Condition/Disease | All Ages | Under 45 | 45-64 | Over 65 | Over 75 | NE | MW | S | W |
| COPD | | | | | | | | | |
| Incidence/1,000 persons | 61 | 50 | 63 | 104 | 107 | 56 | 63 | 63 | 61 |
| No. cases × 1,000 | 15,400 | 8,650 | 3,550 | 3,210 | 1,200 | | | | |
| Asthma | | | | | | | | | |
| Incidence/1,000 persons | 49 | 52 | 45 | 40 | 34 | 48 | 49 | 48 | 52 |
| No. cases × 1,000 | 12,370 | 9,000 | 2,180 | 1,230 | 420 | | | | |
| Heart Disease | | | | | | | | | |
| Incidence/1,000 persons | 86 | 29 | 135 | 325 | 404 | 89 | 84 | 93 | 74 |
| No. cases × 1,000 | 21,600 | 5,050 | 6,540 | 10,000 | 4,980 | | | | |
| HD-ischemic | | | | | | | | | |
| Incidence/1,000 persons | 32 | 3 | 61 | 153 | 184 | 37 | 29 | 37 | 24 |
| No. cases × 1,000 | 8,160 | 490 | 2,970 | 4,702 | 2,270 | | | | |
| HD-rhythmic | | | | | | | | | |
| Incidence/1,000 persons | 33 | 20 | 44 | 83 | 104 | 33 | 35 | 32 | 31 |
| No. cases × 1,000 | 8,160 | 3,500 | 970 | 2,550 | 1,275 | | | | |
| Hypertension | | | | | | | | | |
| Incidence/1,000 persons | 111 | 34 | 226 | 358 | 352 | 106 | 115 | 123 | 91 |
| No. cases × 1,000 | 27,820 | 5,830 | 10,980 | 11,000 | 4,300 | | | | |

Source: National Center for Health Statistics (1994).

they have had more exposure and hence more opportunity to accumulate particles or damage in their lungs.

Cardiorespiratory system function may be compromised and become less efficient in older people and as a result of disease. For example in people over 75 years, 40% have some form of heart disease and 35% have hypertension. Approximately 10% of the population in this age group has COPD. (See table 13-9) Responses to particle inhalation could, conceivably, further compromise the functional status in such individuals. The terminal event(s) of life must presumably result from a triggering or exacerbating of a lethal failing of a critical function, such as ventilation, gas exchange, pulmonary circulation, lung fluid balance, or cardiovascular function in subjects already approaching the limits of tolerance due to preexisting conditions.

### 13.6.2 COPD

The conditions most likely to be affected by inhaled PM are the chronic airways diseases, particularly COPD. COPD is the fourth leading cause of death in the United States, and is the most common cause of non-malignant respiratory deaths, accounting for more than 100,000 deaths in 1993 (National Center for Health Statistics, 1996). According to the International Classification of Disease (ICD) definitions and classification codes, asthma is included along with emphysema, chronic bronchitis, and pnuemonitis under the classification of COPD (490-496). In discussions of epidemiological studies that included this range of ICD codes, asthma is included under COPD unless Code 493 is specifically excluded. In the discussion in Chapters 11 and 13, we have included only emphysema and chronic bronchitis in accord with the view espoused in a recent official statement of the American Thoracic Society (1995).

This group of diseases encompasses emphysema and chronic bronchitis, but information on death certificates may not allow differentiation between these diagnoses. The pathophysiology includes chronic inflammation of the distal airways as well as destruction of the lung parenchyma. Loss of supportive elastic tissue leads to airway closure during expiration, resulting in obstruction of flow. Processes that enhance airway inflammation or edema lead to constriction of the conducting airways or slowing of mucociliary clearance that could adversely affect gas exchange and host defense. Moreover, the uneven matching of ventilation and perfusion characteristic of this disease, with dependence on fewer functioning airways and

alveoli for gas exchange, means inhaled particles may be directed to the remaining functional lung units in higher concentration than in healthy lungs (Bates, 1992)

In comparison to healthy people, individuals with chronic respiratory disease have greater deposition of inhaled aerosols that would be contained in the fine ($PM_{2.5}$) mode (see Chapter 10). The deposition of particles in the lungs of a COPD patient may be as much as three-fold greater than in a healthy adult. Thus, the potential for greater target tissue dose in susceptible patients is present. The lungs of individuals with chronic lung diseases, such as asthma, bronchitis, or emphysema are often in a chronic state of inflammation. In addition to the fact that particles can induce an inflammatory response in the respiratory region, the influence of particles on generation of proinflammatory cytokines is enhanced by the prior existence of inflammation. Phagocytosis by alveolar macrophages is down-regulated both by inflammation and the increased volumes of ingested particles. Therefore, people with lung disease not only have greater particle deposition, but the conditions that exist in their lungs prior to exposure are conducive to amplification of the effects of particles and depression of their clearance.

Particles, especially submicron particles, could also act at the level of the pulmonary vasculature by eliciting changes in pulmonary vascular resistance that could exacerbate ventilation perfusion abnormalities in people with COPD. Emphysema destroys alveolar walls and pulmonary capillaries causing a progressive increase in pulmonary vascular resistance, pulmonary blood pressure, and interstitial edema, eventually leading to systemic hypoxia. This results in an increased workload on the heart and increases the risk of heart failure.

Patients admitted to an intensive care unit for acute COPD exacerbations have a substantial hospital mortality (possibly as high as 25%) rising to an overall mortality that may approach 60% within one year of the admission. For patients 65 years and older, the mortality is substantially higher than for younger patients (Seneff et al., 1995). Mortality is often associated with non-respiratory system organ dysfunction and thus causes of death may be misclassified.

### 13.6.3 Cardiovascular Disease

Particulate pollutants have been associated with increases in cardiovascular mortality both in the historic major air pollution episodes and in the more recent time-series analysis. Approximately eight times as many deaths are caused by heart disease as by chronic respiratory disease. Bates (1992) has postulated three ways in which pollutants could affect cardiovascular mortality statistics. These include: acute airways disease misdiagnosed as pulmonary edema; increased lung permeability, leading to pulmonary edema in people with underlying heart disease and increased left atrial pressure; and acute bronchiolitis or pneumonia induced by air pollutants precipitating congestive heart failure in those with pre-existing heart disease. Moreover, the pathophysiology of many lung diseases is closely intertwined with cardiac function. Many individuals with COPD also have cardiovascular disease caused by: smoking, aging, or pulmonary hypertension accompanying COPD. Terminal events in patients with end-stage COPD are often cardiac, and may therefore be misclassified as cardiovascular deaths. Furthermore, hypoxemia associated with abnormal gas exchange can precipitate cardiac arrhythmias and lead to sudden death.

### 13.6.4 Asthma

Asthma is a common chronic obstructive respiratory disease that may be exacerbated by air pollution. Asthmatics are known to be more sensitive to certain gaseous pollutants such as sulfur dioxide and ozone. General trends in asthma mortality (increasing) have not paralleled changes in air pollution (decreasing) (Lang and Polansky, 1994). Atmospheric particle levels have been linked with increased hospital admissions for asthma, worsening of symptoms, decrements in lung function, and increased medication use. Asthma-related mortality is relatively uncommon, accounting for approximately 5000 deaths annually or about 5% of total chronic respiratory deaths in 1991. Asthma accounts for only a small percentage of overall respiratory death in older adults. Although PM-related mortality may have a component related to asthma, the observed mortality increases cannot be accounted for by increased deaths due to asthma alone.

### 13.6.5 Estimating Public Health Impacts of Ambient PM Exposures in the United States

Efforts to quantify the number of deaths attributable to, and the years of life lost to, ambient PM exposure are currently subject to much uncertainty. Determination of the number of deaths attributable to a risk factor requires knowledge of the following entities: (1) the number of deaths in the population; (2) variations in the extent of exposure of the population to the factor; and (3) the relative risk of mortality that exposure to the factor confers; and (4) the shape of the underlying exposure-response relationship.

In the case of PM exposure, uncertainty arises primarily with regard to the second, third, and fourth entities. While available monitoring information provides rough estimates of likely exposures of the general population or susceptible subpopulations for $PM_{10}$ in a number of U.S. urban locations, much less extensive information exists with regard to ambient measures of $PM_{2.5}$ or other indicators of fine particles or specific PM constituents.

As for the third entity, several sources of uncertainty would affect derivation of and application of population relative risk estimates for PM and mortality. First, risk ratios from various short-term mortality studies, while generally falling within a range of 1.02 to 1.10 (i.e., 2 to 10% increase in risk of death over background risk), do vary somewhat from site to site. Hence, it is probably most credible to use site-specific relative risk estimates in projecting numbers of PM-related health events for any particular U.S. city, rather than broad application of a single "best estimate" relative risk value across various locations. Lastly, the proportions of total PM-mediated mortality attributable to short-term and long-term PM exposure are not known, and the overlap between short-term and long-term mortality studies, that is the proportion of all PM-mediated mortality detected in both types of studies, is not known. Therefore, it would be difficult to achieve appropriate weighting of the widely-divergent short-term and long-term mortality risk ratios in projecting potential PM public health impacts.

The interpretation of the underlying exposure-response relationships is probably the most problematic issue for risk assessment purposes at this time. In the absence of clear toxicologic evidence regarding possible mechanisms of action that would plausibly explain the observed epidemiologic associations between mortality or morbidity and low-level ambient PM concentrations, one is left with a dilemma of how to interpret the underlying exposure-response relationship based only on the available epidemiologic findings.

As shown in Figure 13-5, several alternative interpretations of reported relative risk findings are reasonable with regard to possible underlying PM exposure (concentration)-health effects relationships. Most published studies report results (RR estimates) based on linear models (as illustrated by Line A in the figure), implying a possible linear, no-threshold underlying relationship that may extend to essentially zero PM concentrations (line B). However, the existing PM epidemiology data do not allow one to rule out the possible existence of an underlying non-linear relationship (e.g., the "threshold" function illustrated by Line C). The choice of one or another interpretation for risk assessment purposes has important ultimate implications. Choice of a linear, no-threshold function implied by Line B may overestimate numbers of health events (e.g., numbers of PM-related deaths or hospital visits per day or year), given the absence of evidence substantiating increased risk below the lowest observed PM concentrations used in generating the risk estimates. On the other hand, far fewer health events would be estimated for the lowest PM concentrations before any "threshold" breakpoint if the relationship implied by Curve C is assumed. Another intermediate possibility would be to assume a linear relationship down to an estimated PM "background level", as a means of projecting the number of health events that would be associated with theoretically controllable PM concentrations above "background" levels.

Unfortunately, only very limited information now exists from published analyses that might aid in resolving this interpretational dilemma. As noted earlier, most of the PM epidemiology studies report only the results of fitting a linear model for PM for the relative risk of a health effect for a specific PM increment. Only a few studies provide additional information by which to assess the adequacy of the linear model assumption. Nonlinear smoothing splines have been shown by Schwartz (1994b) and by Samet et al. (1995) for their Philadelphia mortality studies, by Schwartz (1994a) for the Cincinnati mortality study, by Schwartz (1993) for the Birmingham $PM_{10}$ mortality study, and by Schwartz for a number of hospital admissions studies. Linear splines were shown by Cifuentes and Lave (1996) for a different set of Philadelphia TSP mortality data. The TSP mortality curves shown in Chapter 12 are compared in Figure 13-6, along with linear models based in part on the same studies. Both the TSP models fitted without copollutants (Cincinnati, Philadelphia 1973 to 1980) and

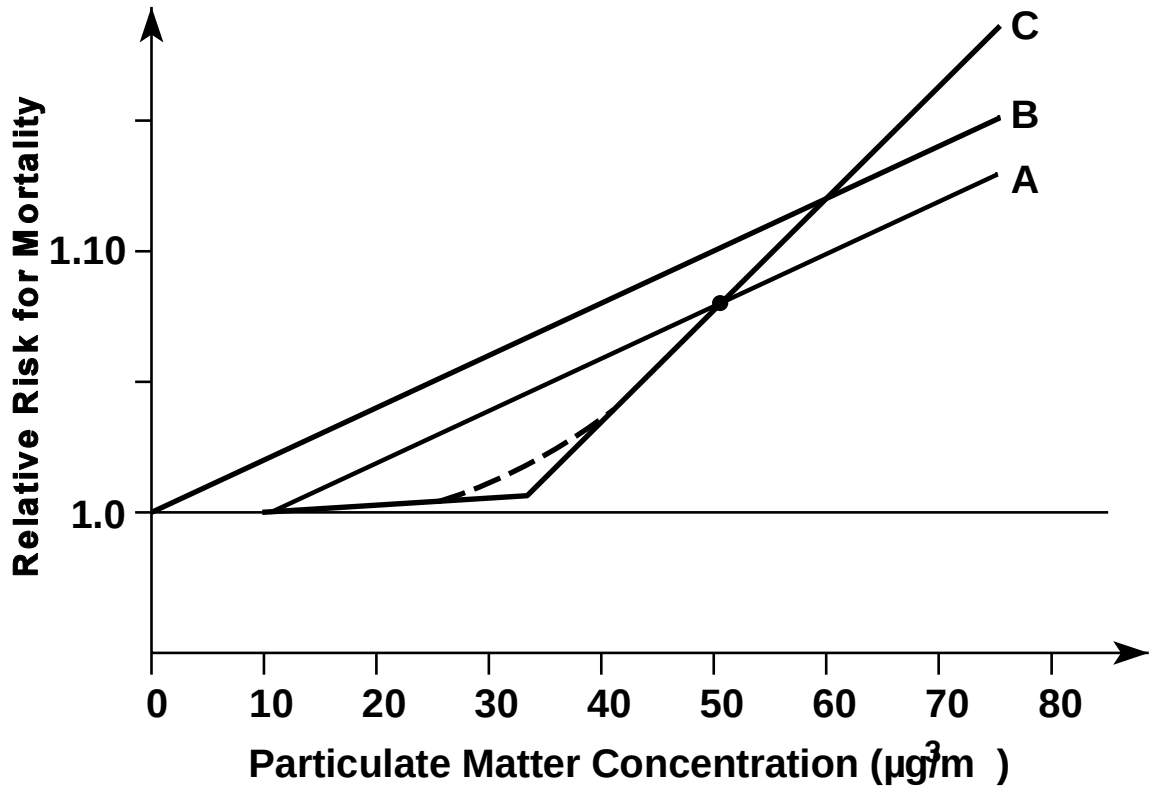


**Figure 13-5. Schematic representation of alternative interpretations of reported epidemiologic relative risk (RR) findings with regard to possible underlying PM mortality concentration-response functions. Published studies typically only report results from linear models that estimate RR over a range of observed PM concentrations as represented by Line A (specific PM values shown are for illustrative purposes only), compared against baseline risk (RR = 1.0) at the lowest observed PM level. One alternative interpretation is that the RR actually represents an underlying linear, no-threshold PM-mortality relationship (Line B) with the same slope as Line A but extending below the lowest observed PM level essentially to 0 $\mu$g/m$^3$. Another possibility is that the underlying functional relationship may have a threshold (illustrated by Curve C), with an initially relatively flat segment, not statistically distinguishable from the baseline risk (1.0) until some PM concentration where it sharply increases (or more likely somewhat less sharply ascends in the vicinity of the breakpoint as shown by the dashed lines).**

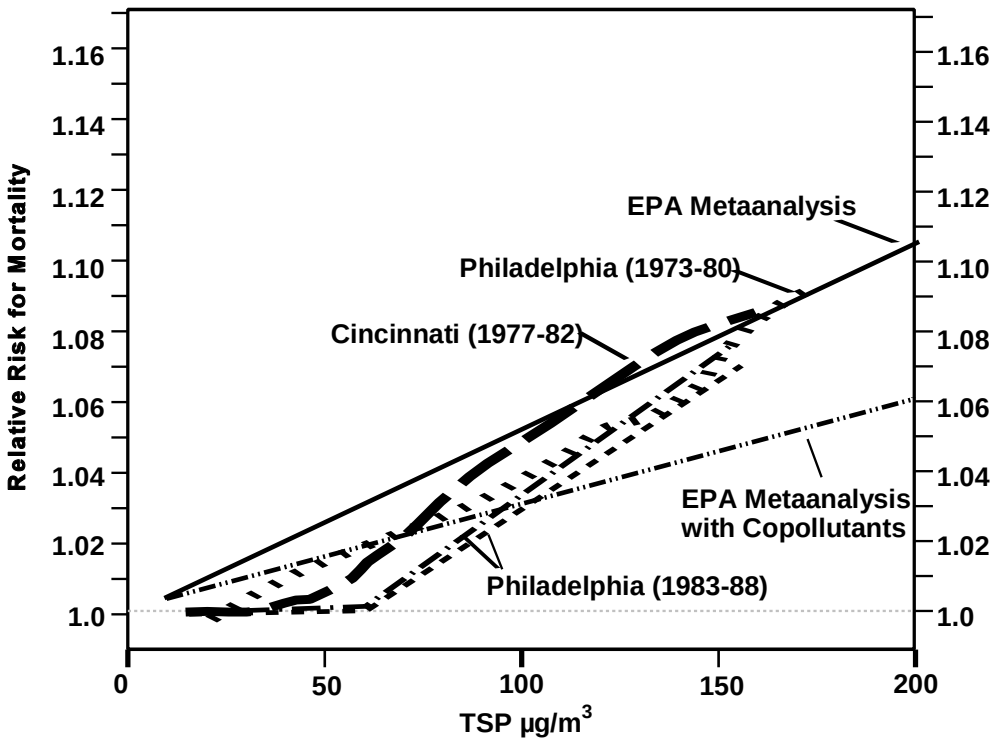


**Figure 13-6. Comparison of smoothed nonlinear and linear mathematical models for relative risk of total mortality associated with short-term TSP exposure. Curves show smoothed nonparametric models for Philadelphia (based on Schwartz 1994b and for Cincinnati (based on Schwartz, 1994a), and piecewise linear models for Philadelphia (based on Cifuentes and Lave, 1996). Solid curve shows linear model from EPA metaanalysis using studies with no copollutants, dash-dot curve shows linear model from EPA metaanalysis using studies with $SO_2$ as a copollutant (described in Chapter 12).**

with copollutants (Philadelphia 1983 to 1988, EPA metaanalysis) show some tendency for a linear model to over estimate mortality at low concentrations and to underestimate mortality at higher concentrations. The differences between linear and nonlinear models are sometimes statistically significant (Samet et al., 1995). Not enough comparisons are available to determine whether nonlinear models may be needed for $PM_{10}$ or $PM_{2.5}$ concentration-effect relationships, but some assessments reported for Birmingham (Schwartz, 1994g) and Utah Valley (Pope and Kalkstein, 1996) find no significant improvement by fitting LOESS models instead of a linear model. Additional tests of the adequacy of the additive linear model for PM and its copollutants

would be desirable. The additive linear model and the corresponding RR estimates appear adequate for assessments of $PM_{10}$ and $PM_{2.5}$ effects.

## 13.7 SUMMARY AND CONCLUSIONS

The chemical and physical differences between fine-mode and coarse-mode particles have important implications for evaluation of the health and welfare effects of such particles as distinct pollutant subclasses. For example, as discussed in Section 13.3, the differences in removal of fine and coarse particles from air streams leads to differences in respiratory tract deposition, although both fine and coarse particles penetrate into and deposit in all regions of the respiratory tract. According to the available empirical evidence and deposition models, particles above 15 $\mu$m are largely removed by impaction in the nose, throat and larynx. The efficiency of removal in this region falls as particle size decreases from 10$\mu$m to 1$\mu$m $d_{ae}$ and reaches a minimum between 0.5 and 0.1 $\mu$m $d_{ae}$. As the particle size decreases below 0.1 $\mu$m $d_{ae}$, the removal efficiency increases again due to diffusion of the very small particles to surfaces. The larger particles in the coarse fraction are deposited more in the tracheobronchial region (TB) and, as particle size decreases, TB deposition decreases and alveolar deposition increases, reaching a peak between approximately 1 and 5 $\mu$m $d_{ae}$. Both TB and alveolar deposition reach a minimum in the accumulation-mode size range between 0.5 and 1.0 $\mu$m $d_{ae}$ with alveolar deposition being greater than TB deposition. For particle sizes below 0.5 $\mu$m $d_{ae}$, both TB and alveolar deposition increase due to diffusion and reach a peak below 0.1 $\mu$m.

Our current understanding of the toxicology of ambient particulate matter suggests that fine and coarse particles may have different biological effects. For example, as discussed more fully in Chapter 11 and Section 13.5, differences in chemical composition of fine and coarse particles lead to the prediction of different biological effects. Acids, metals which generate hydroxyl radicals and reactive oxidant species in the lung, and dissolved reactive species may all be carried into the respiratory tract by fine particles. On other hand, silica (which may produce a distinctive lung pathology) and biological materials such as spores, pollens, bacteria, and other biological fragments which may produce immune responses are found primarily among coarse-mode particles, many of which may be larger than 10 $\mu$m. Some epidemiology studies tend to show stronger associations with fine particle indicators than with coarse particles.

However, clear differentiation between $PM_{2.5}$ and $PM_{10}$ is difficult from currently available analyses and is complicated by the fact that $PM_{2.5}$ is part of $PM_{10}$. Direct assessment of coarse PM effects (i.e., $PM_{15/10}$-$PM_{2.5}$) is especially limited in available epidemiologic studies.

The evidence for PM-related effects from epidemiologic studies is fairly strong, with most studies showing increases in mortality, hospital admissions, respiratory symptoms, and pulmonary function decrements associated with several PM indices. These epidemiologic findings cannot be wholly attributed to inappropriate or incorrect statistical methods, misspecification of concentration-effect models, biases in study design or implementation, measurement errors in health endpoint, pollution exposure, weather, or other variables, nor confounding of PM effects with effects of other factors. While the results of the epidemiology studies should be interpreted cautiously, they nonetheless provide ample reason to be concerned that there are detectable human health effects attributable to PM at levels below the current NAAQS.

There is considerable agreement among different studies that the elderly are particularly susceptible to effects from both short-term and long-term exposures to PM, especially if they have underlying respiratory or cardiac disease. These effects include increases in mortality and increases in hospital admissions. Children, especially those with respiratory diseases, may also be susceptible to pulmonary function decrements associated with exposure to PM or acid aerosols. Respiratory symptoms and reduced activity days have also been associated with PM exposures in some studies.

A number of studies using multiple air pollutants as predictors of health effects have not completely resolved the role of PM as an independent causal factor. PM concentrations are often correlated with concentrations of other pollutants, in part because of common emissions patterns and in part because of weather patterns. There are seasonal differences within any community, however, and differences exist among various communities that allow at least some separation of PM effects from those of other pollutants. Unfortunately, most of the analyses of multiple pollutants within cities have used additive linear models that may not adequately characterize the interactions among pollutants, so that confident assignment of specific fractions of variation in health endpoints to specific air pollutants may still require additional study.

Within the overall PM complex, the indices that have been most consistently associated with health endpoints are fine particles (indexed by BS, COH, and $PM_{2.5}$), inhalable particles

($PM_{10}$ or $PM_{15}$), and sulfate ($SO_4^{=}$). Less consistent relationships have been observed for TSP, strong acidity ($H^+$), and coarse PM ($PM_{10-2.5}$). For reasons discussed above, none of these indices can completely be ruled out as a biologically relevant indicator of PM exposure.

Based on current evidence from epidemiologic, controlled human, human occupational, and laboratory animal studies, no conclusions can be reached regarding the specific chemical components of $PM_{10}$ that may have the strongest biologic activity. Various subclasses of PM have been considered including acid aerosols, bioaerosols, metals (including transition metals), and insoluble ultrafine particles. On the basis of currently available information, none of these can be specifically implicated as the sole or even primary cause of specific morbidity and mortality effects.

Recent analyses have substantiated the previous selection of $PM_{10}$ as an indicator of particle-related health effects. The strong and consistent association of mortality and various morbidity endpoints with $PM_{10}$ exposure clearly demonstrates that this indicator of inhalable particle mass and the associated PM standard are appropriate for the protection of public health.

There is evidence that older adults with cardiopulmonary disease are more likely to be impacted by PM-related health effects (including mortality) than are healthy young adults. The likelihood of ambient fine mode particles being significant contributors to PM-related mortality and morbidity among this elderly population is bolstered by: (1) the more uniform distribution of fine particles across urban areas and their well-correlated variation from site to site within a given city; (2) the penetration of ambient particles to indoor environments (where many chronically ill elderly individuals can be expected to spend most of their time), and (3) the longer residence time of ambient fine particles in indoor air, enhancing the probability of indoor exposure to ambient fine particles more so than for indoor exposure to ambient coarse particles.

In addition to the above rather broad classification of elderly individuals (including ≈50% of adults over 65) as being at special risk, identification of other specific sensitive populations by age group or specific disease entity may also be warranted based on currently available analyses. These clearly include younger (i.e., < 65) individuals with acute or chronic respiratory disease (e.g., pneumonia, COPD, etc.) and/or cardiovascular diseases, current and former smokers (who account for about 80 to 85% of COPD deaths and many cardiovascular disease deaths), and possibly young children in regard to acute pulmonary function decrements being induced by low level PM exposures.

The above-noted differences indicate that it would be appropriate to consider fine and coarse mode particles as separate subclasses of pollutants. For this reason it would be desirable to monitor each class separately. Because fine and coarse particles are derived from different sources, it is also necessary to quantify ambient levels of fine and coarse particles separately in order to plan effective control strategies.

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